Redefiniendo el consentimiento informado en investigación biomédica.

Tesis Doctoral. Programa de Doctorado en Estudios Históricos y Sociales sobre Ciencia, Medicina y Comunicación Científica

Doctorando: Jaime Fons Martínez

Directores de la tesis:

- **Dr. Josep Lluis Barona Vilar**
- **Dr. Javier Díez Domingo**

Fecha de depósito: Enero 2023

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 741856.

AGRADECIMIENTOS

Largo ha sido el camino que me ha llevado a poder, hoy, presentar mi tesis doctoral y durante este proceso varias han sido las personas e instituciones que han hecho que esta sea posible tanto a nivel científico como económico y afectivo/emocional.

Primero debo agradecer a la Comisión Europea y a FISABIO por haber sido quienes han posibilitado que esta investigación se lleve a cabo y que yo haya sido investigador y coordinador técnico del proyecto i-CONSENT, en el cual se engloba esta tesis doctoral.

Asimismo quiero agradecer a las distintas entidades e investigadores que han participado en dicho proyecto por su trabajo, dedicación y compañerismo que han permitido que i-CONSENT haya sido un éxito. Ha sido un gran placer haber compartido con vosotros estos 4 años en los que además de duro trabajo e interesantes y enriquecedoras discusiones, de las que he aprendido mucho, también ha habido momentos de risas y entretenimiento como parte de las reuniones presenciales, aunque la COVID-19 no nos haya permitido hacer un evento final y una despedida a la altura.

Por supuesto he de reconocer y agradecer a mis tutores, los doctores Josep Lluis Barona Vilar y Javier Díez Domingo, por haber aceptado dirigirme esta tesis y por el continuo trabajo de mentorización y apoyo realizado. En el caso de Javier, con quien he compartido el día a día, además quiero agradecerle el haberme dado esta increíble oportunidad laboral, que me ha permitido crecer muchísimo y el que siga confiando en mí tras el proyecto i-CONSENT con nuevos proyectos, permitiéndome consolidarme y sentirme importante en el equipo. Muchas gracias por tu constante apoyo, por fomentar la confianza en mí mismo y en mi trabajo, mostrándote paciente y comprensivo en los errores y elogiando los aciertos, permitiéndome asumir cada vez más responsabilidades y animándome a seguir creciendo profesionalmente, ir formando mi equipo de trabajo y no tener miedo a salir de mi zona de confort. Gracias por tu apoyo tanto a nivel profesional como personal y a todo lo que me han enseñado.

Gracias a mis compañeros y compañeras, presentes y pasados, del Área de Investigación en Vacunas (AIV), trabajar con vosotros es un gran placer, hacéis que el trabajo sea más que eso. Sois un equipo de una gran calidad profesional y humana, con los que además de aprender me divierto.

Gracias especialmente a Mónica Vázquez, por "enseñarme a andar" en los proyectos internacionales y haberme acompañado en los primeros años del i-CONSENT, has sido una gran compi de despacho, de viaje, de preocupaciones y de alegrías. Sin duda eres una de las personas de las que más he aprendido, tienes mi eterna admiración y gratitud.

Gracias Cristina por tu ayuda y acompañamiento en el proyecto, en los viajes y congresos, y en varios de los artículos que componen esta tesis, y gracias por los cruasanes que traías a las reuniones.

Gracias Lina, últimamente Jacobo, y desde mis orígenes en FISABIO y de forma muy especial Ana Molina, por animarme (y presionarme) a hacer y acabar la tesis. Gracias por las largas

conversaciones, los poco habituales almuerzos y las risas, y gracias por aceptar embarcaros conmigo en presentes y futuros proyectos.

Y por supuesto, las gracias más especiales:

A mi familia, mi mujer Jenny y mis hijos Jaume y Martina por vuestro amor y cariño, por hacerme feliz cada día y darle sentido a todo lo que hago. Sin vosotros nada de esto, en ninguno de sus sentidos habría sido posible. Mis padres, Jaime y Rosario, por todo el apoyo y cariño que me lleváis dando desde el día de mi nacimiento hasta hoy y por ser tan tremendamente buenos padres, indudablemente parte de esta tesis y de todos los logros en mi vida son vuestros. Mis hermanos, Marito y Arturo, porque me habéis ayudado a ser quien soy a día de hoy, me habéis apoyado en todo lo que he necesitado y sé que siempre estáis y estaréis ahí. Os quiero muchísimo.

Y a mis amigos, todos, pero especialmente Josep, Pedro, Toni y Piki, prácticamente toda una vida juntos. No sois conscientes de lo importante que es para mí quedar con vosotros y como me ayuda a equilibrar mi vida y me da energías para encarar las semanas de trabajo. En una carrera de fondo como una tesis, aunque indirectamente, sois fundamentales.

Muchas gracias a todos/as.

Contenido

INTRODUCCION

El proceso de consentimiento informado es un pilar fundamental como garante de la autonomía del participante en investigación clínica. Durante este proceso, el potencial participante recibe la información necesaria para poder tomar una decisión informada sobre si quiere participar o no en una investigación. Incluye información detallada sobre los propósitos y métodos de la investigación, los posibles beneficios y riesgos inherentes a la participación o el derecho a retirarse del estudio en cualquier momento sin tener que dar ninguna explicación, entre otras, además el investigador debe comprobar que el potencial participante ha comprendido adecuadamente esta información.

La idea sobre la que se construye el consentimiento informado actual tiene su origen en la filosofía política construida a lo largo de la Modernidad (s.XVI-XIX), que cuestionó que las relaciones humanas se basen en una relación vertical en la que uno manda y otro obedece pasivamente. Aun así, esta no llegó a la medicina hasta mediados del siglo XX, suponiendo un cambio de paradigma y pasando de una práctica médica paternalista a una relación basada en el principio de autonomía, donde el paciente toma las decisiones tras ser informado por su médico sobre las distintas opciones de tratamiento, prevaleciendo su consideración de ciudadano, con derecho a la información y a la toma de decisiones sobre su salud [1, 2].

Varios autores[3,4] identifican la Primera (1891) y la Segunda (1900) Directriz Prusiana sobre Investigación como los antecesores a los consentimientos informados actuales en investigación. Estas Directrices regulaban respectivamente la investigación con presidiarios; y las intervenciones médicas que no tuviesen como fin el diagnóstico, tratamiento o inmunización. En ellas se incluía el requisito del consentimiento para ser tratado con un tratamiento experimental. Además, la Segunda Directriz indicaba que en este tipo de intervenciones no podían participar ni menores de edad, ni personas consideradas como mentalmente incompetentes. Paralelamente, la Comisión Reed (comisión del ejército estadounidense, comandada por Walter Reed, y formada para estudiar el modo de transmisión de la fiebre amarilla), en sus investigaciones llevadas a cabo en Cuba (1900), incluyó un documento en forma de contrato en el que se explicaban los riesgos de participar en el estudio, que no existía un tratamiento efectivo frente a la enfermedad y expresaba la

[1] Simón P. Diez mitos en torno al consentimiento informado. An Sist Sanit Navar. 2006; 29 (2):29-40.
[2] De Siqueira JE. *Los orígenes del consentimiento informado en clínica*. Revista de Bioética Latinoamericana. 2009; 3(1).
[3] Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. BMJ. 1996;313(7070):1445-9.
[4] Suárez-Obando F; Ordoñez A. *Ética de la Investigación científica: la fiebre amarilla, la Comisión Reed y el origen del consentimiento informado*. Infectio. 2010;14(3):206-16.

voluntariedad del sujeto para participar en la investigación y las condiciones en las que esta se daba[5].

Tras la Segunda Guerra Mundial, el Código de Núremberg (1947), que recoge los 10 principios que rigen la experimentación con seres humanos, marcó un punto de inflexión en la historia de la ética de investigación médica tras los abusos sin ningún tipo de regulación nacional o internacional que tuvieron lugar especialmente en los campos de concentración por parte de los médicos de la Alemania nazi. Algunos autores consideran este código como el documento más importante de la historia en este campo[6], mientras que otros, pese a reconocer su importancia, critican su falta de originalidad y señalan que 6 de sus 10 principios (incluyendo el de la necesidad de consentimiento informado) derivan de las Guías para Experimentación de Humanos, dictadas en 1931 durante la República de Weimar.[7]

Siguiendo la estela del Código de Núremberg, la Asociación Médica Mundial (AMM) aprobó los "Principios para los que investigan y experimentan" (1954) y la "Declaración de Helsinki" (1964)[8]. Esta Declaración da gran importancia al consentimiento informado, término que aparece por primera vez en un documento de ética de la investigación médica en su primera revisión (Tokio, 1975). En dicha segunda versión de la Declaración también se introdujo la necesidad de la supervisión y aprobación del protocolo del estudio por un comité independiente antes del comienzo del estudio, a diferencia del Código de Nuremberg, que dejaba esta solicitud de consentimiento dentro de la relación deontológica entre el médico y el paciente[9].

Pese al esfuerzo realizado por la AMM, el consentimiento informado no se convirtió en una práctica habitual hasta la publicación del Informe Belmont en 1979.[10] Dicho Informe se dividía en tres partes: (a) límites entre la práctica y la investigación, donde explica las diferencias entre ellas; (b) principios éticos básicos, donde define los tres principios éticos básicos que son: el respeto a las personas, la beneficencia y la justicia; (c) los requisitos que implica la aplicación de los principios generales, que son el consentimiento informado, la evaluación de riesgos y beneficios y la selección de sujetos. Además, el Informe indica que el consentimiento

[5] Suárez-Obando F; Ordoñez A. *Ética de la Investigación científica: la fiebre amarilla, la Comisión Reed y el origen del consentimiento informado*. Infectio. 2010;14(3):206-16.
[6] Shuster E. Fifty years later: the significance of the Nuremberg Code. N Engl J Med. 1997;337(20):1436-40
[7] Ghooi RB. The Nuremberg Code–A critique. Perspect Clin Res. 2011; 2(2): 72–76.
[8] World Medical Assembly. Declaration of Helsinki. Recommendations guiding doctors in clinical research. Finland: World Medical Association. 1964. https://www.wma.net/wp-content/uploads/2018/07/DoH-Jun1964.pdf
[9] Palazzani L. Informed Consent, Experimentation and Emerging Ethical Problems. BioLaw Journal , Special Issue 1/2019:11-22.
[10] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, Belmont, 1979.

informado se basa en la Información, la Comprensión y la Voluntariedad, e indica que los investigadores son responsables de asegurarse de que el sujeto ha comprendido la información facilitada.

Desde la publicación del Informe Belmont, la ética en investigación médica ha seguido avanzando. Especialmente relevantes han sido las contribuciones de las Directrices de la Conferencia Internacional de Armonización (ICH) para la buena práctica clínica[11] (1996, desde 2021 están trabajando en una última revisión); las guías éticas del Council for International Organizations of Medical Sciences (CIOMS)[12] (1982, última revisión 2016) y las revisiones de la Declaración de Helsinki[13] (cuya última versión, de 2013, es su novena revisión).

Pese a todos estos avances, hay una serie de retos que persisten a día de hoy en el consentimiento informado, incluyendo que:

- Son documentos largos, utilizan jerga profesional y son difíciles de comprender [14, 15].
- Suele prepararlo el promotor, teniendo en cuenta sus propios intereses y sin considerar los puntos de vista del resto de partes interesadas. Dando lugar a documentos más defensivo que realmente informativos. [16]
- Muchas veces se considera el consentimiento informado como un acto legal y burocrático centrado sobre todo en el acto puntual de la firma. Actualmente existe una tendencia a intentar evitar esta percepción, fomentando que el consentimiento se entienda como un proceso[17] y cuestionando la idea de que la firma implique intrínsecamente una adecuada comprensión de la información[18].

[11] European Medicines agency. ICH E6 (R2) Good Clinical Practice. Disponible en: https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice. Citado el 11/02/2022.
[12] Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Health-related Research Involving Humans. Switzerland: CIOMS; 2016.
[13] Asociación Médica Mundial. Declaración de Helsinki de la AMM – Principios éticos para las investigaciones médicas en seres humanos. October 2013. https://www.wma.net/es/policies-post/declaracion-de-helsinki-de-la-amm-principios-eticos-para-las-investigaciones-medicas-en-seres-humanos/
[14] Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G. Informed consent: how much and what do patients understand? Am J Surg. 2009;198(3):420-35.
[15] Tam NT, Huy NT, Thoa le TB, Long NP, Trang NT, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93(3):186-98H.
[16] Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. N Engl J Med. 2017 Mar 2;376(9):856-867. doi: 10.1056/NEJMra1603773.
[17] Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Health-related Research Involving Humans. Switzerland: CIOMS; 2016.
[18] Shah P, Thornton I, Turrin D, et al. Informed Consent. [Updated 2021 Jun 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

- Pese a la creciente importancia que se da a la inclusión de personas con distintas características y antecedentes en investigación,[19] los materiales para el consentimiento informado suelen realizarse a partir de plantillas estandarizadas, que no tienen en cuenta las necesidades, intereses y características de los potenciales participantes. La no adaptación de la información a las características de la persona receptora, conlleva un mayor riesgo de que no la entienda correctamente y no pueda tomar una decisión autónoma.[20]
- Los avances tecnológicos y nuevas formas de comunicación tienen un gran potencial en el consentimiento informado, como el uso de materiales digitales y multimedia en el consentimiento informado, pero también conllevan nuevos retos en términos de divulgación, comprensión, voluntariedad y autorización[21].
- El uso, cada vez más habitual, de las redes sociales durante el reclutamiento de participantes, también conlleva retos éticos para los que no hay una respuesta clara y consensuada. Esta modalidad de reclutamiento requiere aplicar de normas legales y éticas en un contexto que puede resultar desconocido para los investigadores y los comités de ética.[22]
- La comunicación investigador – potencial participante es un factor clave, tanto para la comprensión del consentimiento informado como para la satisfacción de los potenciales participantes, su influencia e importancia en el proceso de consentimiento informado puede ser mayor, incluso, que la información en formato escrito.[23,24] Sin embargo el personal investigador no suele entrenar estas habilidades y tiende a sobrestimar sus capacidades en este campo.[25]

En el año 2015, la Comisión Europea se hizo eco de estas dificultades y retos y de la necesidad de mejorar el proceso de consentimiento informado, sobre todo respecto a su comprensión,

[19] Gray DM 2nd, Nolan TS, Gregory J, Joseph JJ. Diversity in clinical trials: an opportunity and imperative for community engagement. Lancet Gastroenterol Hepatol. 2021 Aug;6(8):605-7. doi: 10.1016/S2468-1253(21)00228-4.
[20] Bento SF, Hardy E, Osis MJ. Process for obtaining informed consent: women's opinions. Dev World Bioeth. 2008;8(3):197-206.
[21] Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. N Engl J Med. 2017 Mar 2;376(9):856-867. doi: 10.1056/NEJMra1603773.
[22] Gelinas L, Pierce R, Winkler S, Cohen IG, Lynch 594 HF, Bierer BE. Using Social Media as a Research Recruitment Tool: Ethical Issues and Recommendations. Am J Bioeth. 2017;17(3):3-14. doi:10.1080/15265161.2016.1276644
[23] Hayman RM, Taylor BJ, Peart NS, Galland BC, Sayers RM. Participation in research: Informed consent, motivation and influence. J Paediatr Child Health. 2001;37:51-4.
[24] Stevens PE, Pletsch PK. Informed consent and the history of inclusion of women in clinical research. Health Care Women Int. 2002;23(8):809-19
[25] Ha JF, Longnecker N. Doctor-Patient Communication: A Review. The Ochsner Journal. 2010;10(1):38-43

que no había mejorado significativamente en las últimas tres décadas,[26] y publicó la convocatoria de la propuesta SwafS-17-2016, titulada "La ética del consentimiento informado en los nuevos tratamientos, incluida la perspectiva de género"[27]. El proyecto “Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective (i-CONSENT)” resultó financiado en dicha convocatoria (acuerdo de consorcio 741856).

Esta tesis doctoral por compendio de artículos presenta algunos de los principales resultados, aprendizajes y experiencias de dicho proyecto, del que el doctorando era coordinador técnico y en el que ha tenido un papel fundamental, liderando 1 de los 3 paquetes de trabajo científicos del proyecto (y sus 5 tareas) y una tarea en cada uno de los otros dos paquetes de trabajo científicos.

En esta tesis se presentan 6 artículos científicos (anexos 1 - 6). Además de estos artículos, en la tesis se incluyen una serie de documentos adicionales que permiten conocer mejor el trabajo realizado por el doctorando durante el proyecto y la profundidad de las recomendaciones y cambios propuestos para mejorar el proceso del consentimiento informado (anexos 7 - 10).

Los artículos que presentan el cuerpo principal de esta tesis son:

- Fons-Martínez J, Ferrer-Albero C, Russell R, Rodgers E, Glennie L, Díez-Domingo J. i-CONSENT: Presentation of the Project and the Importance of Participants’ Perspectives in the Informed Consent Process. BioLaw Journal. 2019 (Special Issue):3-10. (Anexo 1)
- Fons-Martínez J, Calvo Rigual F, Díez-Domingo J, Nepi L, Persampieri L, Ferrer-Albero C. Contents of the Minor’s Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements. BioLaw Journal. 2019(Special Issue):37-52 (Anexo 2)
- Gesualdo F, Daverio M, Palazzani L, Dimitriou D, Diez-Domingo J, Fons-Martinez J, Jackson S, Vignally P, Rizzo C, Tozzi AE. Digital tools in the informed consent process: a systematic review. BMC Med Ethics. 2021;22;18 (Anexo 3)
- Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies. BMC Med Ethics. 2021;22;138. (Anexo 4)

[26] Tam NT, Huy NT, Thoa le TB, Long NP, Trang NT, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93(3):186-98H.

[27] https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/swafs-17-2016

- Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Keys to improving the informed consent process in research: Highlights of the i-CONSENT project. Health Expect. 2022 Aug;25(4):1183-1185. (Anexo 5)
- Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Co-creation of information materials within the assent process: from theory to practice. Health Expect. 2022 Nov 23. doi: 10.1111/hex.13675. (Anexo 6)[28]

Los materiales adicionales son:

- Fons-Martinez J, Diez-Domingo J (editors). Guidelines for Tailoring the Informed Consent Process in Clinical Studies. Valencia: FISABIO. 2021. DOI: 10.5281/zenodo.4563938 (Anexo 7). Este documento es el principal producto final del Proyecto i-CONSENT y del paquete de trabajo 3, siendo la parte central del entregable 3.3. En él se incluye la descripción del nuevo concepto del proceso de consentimiento informado y las recomendaciones para poder llevarlo a cabo. Las guías pretenden cambiar la forma de concebir el consentimiento informado, recogiendo la óptica de las distintas partes interesadas y, sobre todo, poniendo el centro en el potencial participante.
- Enguer-Gosálbez P, Fons-Martínez J, Martínez-Santamaría J, Torres-Redondo AM, Villena-Portella C, García-Robles A, Díez-Domingo J. How Spanish biobanks have adapted the informed consent process during the Covid-19 pandemic. BioLaw Journal, Special Issue 2/2021:121-38 (Anexo 8). El artículo describe cómo los biobancos españoles han adaptado el proceso de consentimiento informado durante la pandemia por COVID-19.
- Deliverable D1.2. Report on gender and age-related issues associated with the acquisition of informed consent (Anexo 9). Este entregable analiza aspectos relativos al género y la edad en el consentimiento informado. Por un lado, mediante una revisión narrativa de la literatura, se realiza un análisis de las diferencias en la comunicación por razones de género; por otro lado se realiza una revisión sistemática de la literatura sobre tres de los aspectos clave en el proceso de toma de decisiones de los menores en los ensayos clínicos: la información que debe darse al menos, cómo evaluar la comprensión de dicha información y cómo evaluar la competencia del menor para tomar la decisión.

[28] Artículo aceptado el 10 de noviembre de 2022 por la revista Health Expectations. El anexo 6 incluye la carta de aceptación de la revista así como la versión del artículo enviada para dicha revisión.

- El uso de las redes sociales para el reclutamiento de participantes en ensayos clínicos: perspectiva de los comités de ética (CEI/CEIm) (Anexo 10). Esta ponencia realizada en el Congreso de la Asociación Nacional de Comités de Ética incluye parte de los resultados de un grupo nominal realizado con miembros de distintos comités de ética de investigación en el que se les preguntaba sobre las principales barreras y oportunidades del uso de la redes sociales para reclutar participantes en ensayos clínicos.

JUSTIFICACIÓN DE LA INVESTIGACIÓN:

Existen múltiples textos éticos y legales que destacan la importancia del consentimiento informado en investigación médica. Estos marcan tanto los contenidos que debe tener como el modo en el que se debe presentar la información o la responsabilidad del investigador de comprobar la correcta comprensión del potencial participante de la información dada.

La realidad del consentimiento informado suele distar bastante de la idea para la que fue concebido: ser un proceso centrado en el potencial participante y que busca capacitarlo para tomar una decisión de forma informada y sin ningún tipo de coacción o influencia indebida. En muchos casos es reducido a un acto burocrático y un requisito ético y legal, centrado en la obtención de la firma por parte del participante que muestre su aceptación a participar. Esto ocasiona que a menudo la información que se le facilite se corresponda más a las necesidades del promotor y a "lo que marca la ley" que a la información que le interesa recibir a los potenciales participantes (resultando en muchos casos en documentos defensivos), además los textos suele ser largos y utilizar un lenguaje difícil de comprender, lo que provoca que la decisión de participar (o no) frecuentemente se tome en base a una conversación entre el potencial participante y el investigador. Paradójicamente, en los ensayos clínicos todo se monitoriza excepto la conversación en la que se informa al participante y en base a la cual este suele tomar la decisión de participar.

Este escenario evidencia la necesidad de realizar una investigación que profundice en distintos aspectos del proceso de consentimiento informado y haga unas recomendaciones que le permitan recuperar su esencia, adaptándolo a las necesidades y preferencias de la población a la que van dirigidos, mejorando su comprensión y ayudando al personal investigador en ese proceso que debe ser de comunicación bidireccional y continua. Asimismo, es importante identificar acciones concretas que permitan llevar a cabo las recomendaciones que aparecen en los distintos documentos éticos y legales ya existentes y que complementen a estos.

Con esta ambición nace el proyecto europeo i-CONSENT y esta tesis doctoral.

OBJETIVOS:

A continuación se presenta el objetivo general de esta investigación, así como sus objetivos específicos.

Objetivo general:

Dar unas recomendaciones para mejorar el proceso de consentimiento informado, haciendo que sea más fácil de comprender y se adapte mejor a las necesidades y preferencias de los potenciales participantes.

Objetivos específicos:

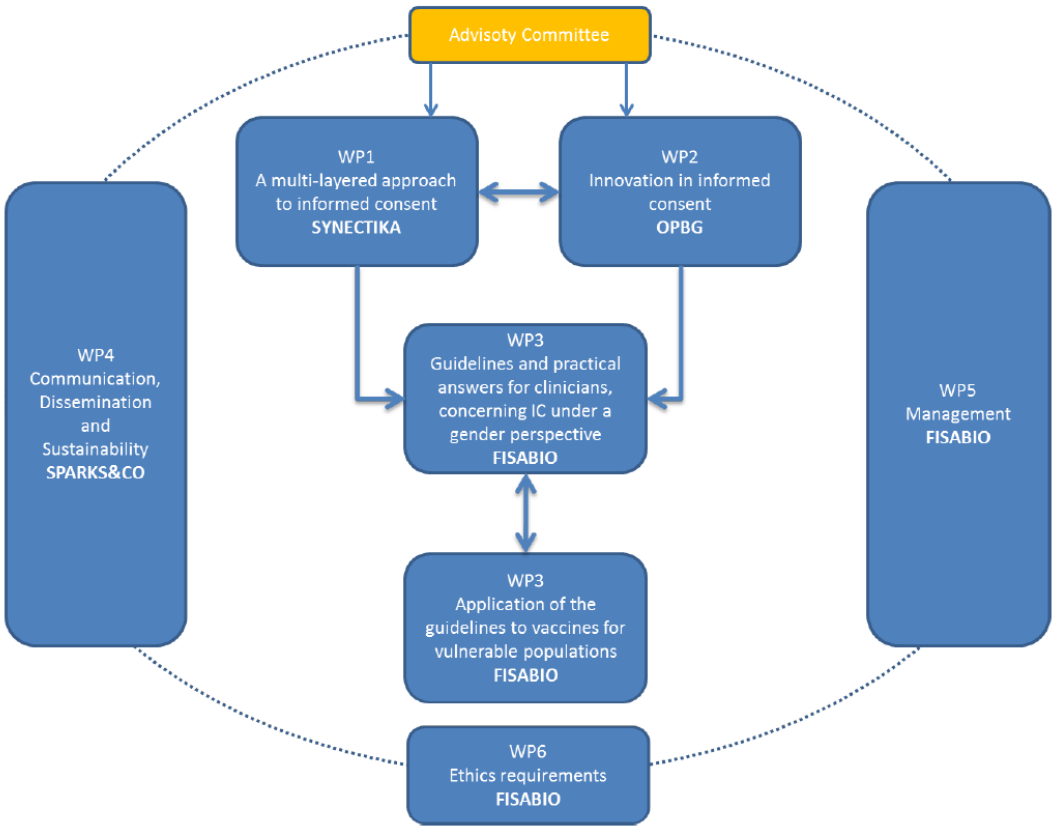
1. Definir el proceso de consentimiento informado y las fases que lo componen
2. Examinar la perspectiva de representantes de los pacientes respecto al consentimiento informado
3. Analizar los contenidos que debe tener el asentimiento informado desde la perspectiva de legisladores, investigadores, padres y madres de los menores y los propios menores.
4. Analizar el uso de las tecnologías digitales en el consentimiento informado.
5. Evaluar la idoneidad de las principales recomendaciones contenidas en las guías por expertos representativos de las principales partes interesadas.
6. Elaborar los materiales de consentimiento de un ensayo clínico hipotético siguiendo las recomendaciones contenidas en las guías.

Estos objetivos representan únicamente una parte de los objetivos del proyecto europeo i-CONSENT y hacen mención a los desarrollados en los artículos presentados en este trabajo de tesis. Para obtener más información sobre el proyecto se puede visitar su web (https://i-consentproject.eu/) y la sección del portal CORDIS de la Comisión Europea dedicada a él (https://cordis.europa.eu/project/id/741856) .

METODOLOGÍA:

Para entender mejor esta tesis es importante entender cómo se estructura el proyecto i-CONSENT. Tiene 6 paquetes de trabajo, 3 de ellos son paquetes de trabajo científicos mientras que los otros 3 son de coordinación, diseminación y aspectos éticos del estudio, tal y como se ilustra en la figura 1:

Figura 1. Diagrama PERT que muestra los diferentes paquetes de trabajo de i-CONSENT y sus interdependencias



Fuente: Acuerdo de consorcio del proyecto i-CONSENT. Grant Agreement 741856. Description of the Action – Part B.

El paquete de trabajo 1 analiza la literatura relativa al consentimiento informado desde distintas perspectivas, incluyendo la literatura científica y los textos éticos y legales, el análisis presta una especial atención a la comunicación y a aspectos de género y edad (menores). Además, se exploró la perspectiva de los pacientes y de representantes de las distintas religiones sobre el consentimiento informado mediante metodologías cualitativas con representantes de estas. Los primeros dos artículos de esta tesis se enmarcan en este paquete de trabajo.

El paquete de trabajo 2 analiza la influencia de las nuevas tecnologías en el proceso de consentimiento informado y diseña estrategias innovadoras para hacer frente a distintos retos que presenta el consentimiento informado en la actualidad. Para ello se realizaron revisiones

sistemáticas de la literatura; análisis de redes sociales y páginas web; encuestas y grupos de design thinking. El tercer artículo de esta tesis pertenece a este paquete de trabajo.

El tercer y último paquete de trabajo científico aunó todo el conocimiento generado en los dos paquetes de trabajo anteriores y, a partir de él, se realizó una nueva definición del proceso de conocimiento informado y recomendaciones para mejorar cada una de sus fases. Estas recomendaciones se presentaron en unas guías que fueron validadas tanto por expertos representativos de las distintas partes interesadas (artículo cuarto presentado en esta tesis) como en la población, para lo que se elaboraron los materiales de 4 consentimientos informados destinados a 4 poblaciones distintas. 3 de estos materiales correspondían a ensayos clínicos ficticios y fueron validados en 3 países distintos y el cuarto correspondía a un ensayo clínico real realizado en la Comunitat Valenciana (estudio VIGIRA). Las validaciones se hicieron mediantes adaptaciones del Quality of Informed Consent Questionnaire (QuIC).[29] Estos materiales, que sirven como ejemplo de la puesta en práctica de las recomendaciones, fueron elaborados mediante co-creación con representantes de la población diana (design thinking, entrevistas, encuestas on line) y se puede acceder a ellos en las siguientes páginas web: http://iconsent.pilotvalidation.eu/ para los materiales de los ensayos clínicos ficticios y https://estudiovigira.es/ para los materiales del ensayo clínico real. En este paquete de trabajo se situarían los 3 artículos restantes.

El trabajo realizado en estos paquetes de trabajo ha permitido analizar el consentimiento informado desde ángulos y perspectivas muy diversas y escuchar a representantes de las principales partes interesadas en el proceso de consentimiento informado en investigación médica.

Una vez situados los distintos artículos que conforman esta tesis en el conjunto del proyecto i-CONSENT, a continuación se explica brevemente la metodología utilizada en cada uno de ellos. Para obtener una información más detallada de cada uno se puede consultar los artículos en cuestión (Anexos 1 - 6).

i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process (Anexo 1):

Este artículo analiza el consentimiento informado a partir de la literatura revisada en el paquete de trabajo 1. Además, muestra las conclusiones del grupo nominal realizado con 8

[29] Joffe S, Cook F, Cleary P, Clark J, Weeks J. Quality of informed consent: a new measure of understanding among research subjects. J Natl Cancer Inst 2001;93:139–47.

representantes de asociaciones de pacientes de 5 países diferentes (Reino Unido, Italia, España, Irlanda y los Países Bajos) (ver entregable D1.6 del proyecto i-CONSENT para más detalles sobre la sesión y metodología utilizada). La sesión del grupo nominal se centró en cuatro temas en torno al consentimiento informado: la comprensión, las expectativas de participación del paciente, el asentimiento en el caso de los menores y la perspectiva de género. El uso de la técnica cualitativa del grupo nominal permitió recoger de una forma muy estructurada las perspectivas de los representantes de los grupos de pacientes respecto a las cuestiones planteadas en torno al proceso de consentimiento informado y que los participantes priorizasen qué aspectos consideraban los más importantes.

Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements (Anexo 2)

En este artículo se compara los contenidos que se considera debe tener el consentimiento informado para menores (asentimiento) según la legislación y la literatura científica.

El análisis de la legislación se realiza mediante un enfoque sistemático, teniendo en cuenta las leyes internacionales, europeas y nacionales de 6 países (Alemania, Austria, España, Francia, Italia y Reino Unido) a partir de 2001. Las bases de datos utilizadas fueron Eurlex para el derecho europeo y las medidas de transposición en la normativa nacional; IURE para la jurisprudencia europea; n-Lex para la normativa nacional sobre el consentimiento; Iurifast y Dec Nat para la jurisprudencia de los Estados miembros que trata de la aplicación del Derecho de la UE; y el Portal Común de la Jurisprudencia para la jurisprudencia nacional.

Respecto a la literatura científica se realizó una búsqueda sistemática con PubMed de artículos experimentales, observacionales y teóricos (se excluyeron los informes de casos); publicados en inglés o español; durante los últimos 10 años (búsqueda realizada el 10 de julio de 2017); que incluyesen aspectos sobre la información que se da o debe darse al menor durante el proceso de asentimiento informado[30]. La revisión de los artículos resultantes de la búsqueda se hizo de forma independiente por dos personas (por título y resumen), las discrepancias fueron resueltas por una tercera persona. Se realizó una lectura crítica y resumen de los

[30] La estrategia de búsqueda utilizada fue: (((“Informed consent”[Mesh] OR “assent”[All Fields]) AND “Ethics”[Mesh] AND (“Research”[Mesh] OR “clinical research”[All Fields])) OR ((“Informed Consent By Minors”[TW] OR “Consent Forms”[TW] OR “assent”[All Fields]) AND (“Ethical Theory”[TW] OR “Principle-Based Ethics”[TW] OR “Ethics,Research”[TW] OR “Research”[TW] OR “Clinical research”[All Fields]))) AND (English[lang] OR Span-ish[lang]) AND (“infant”[TW] OR “child”[TW] OR “adolescent”[TW] OR “minors”[TW]) AND (“2007/07/14”[PDat]: “2017/07/10”[PDat]).

artículos seleccionados, con asignación de calidad del artículo, utilizando las Herramientas de Valoración Crítica de Osteba[31].

Los resultados de ambas búsquedas se expusieron y compararon.

Digital tools in the informed consent process: a systematic review (Anexo 3)

Para esta revisión sistemática de la literatura se buscaron estudios publicados entre el 1 de enero de 2012 y el 31 de octubre de 2020 en las bases de datos electrónicas Pubmed, Embase y Cochrane. La estrategia de búsqueda se realizó a partir del término "Informed Consent" y se combinó con palabras clave o términos Mesh relacionados con tecnologías consideradas relevantes para procesos de Consentimiento Informado innovadores y con soporte digital, como ordenador, computarizado, ayudas audiovisuales, smartphone, mhealth, telemedicina, sistemas online, aplicación móvil o multimedia. Se examinó la lista de referencias de las revisiones publicadas en busca de los artículos que cumplieran los criterios de elegibilidad y que comparasen el efecto de procedimientos digitales de los consentimientos informados frente a las formas no digitales de estos. Los artículos resultantes de analizaron para evaluar el impacto de los componentes digitales del consentimiento informado en la comprensión y satisfacción de los participantes.

Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies (Anexo 4)

Este estudio evalúa el nivel de acuerdo de un panel de expertos representativos de las diferentes partes interesadas con las recomendaciones para mejorar el proceso de consentimiento informado en investigación médica, extraídas de las guías i-CONSENT ("Guidelines for Tailoring the Informed Consent Process in Clinical Studies", Anexo 7). La evaluación se realizó a partir de una adaptación del Método de Adecuación RAND/UCLA[32].

El panel de expertos estaba formado por 14 representantes de diferentes partes interesadas, incluyendo pacientes, reguladores, investigadores, expertos en ética y la industria farmacéutica. Los participantes fueron seleccionados en función de su experiencia en instituciones relevantes o por su relevancia en la literatura científica.

[31] http://www.lecturacritica.com
[32] Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The Rand/UCLA appropriateness method user's manual. Santa Monica, CA: RAND Corporation; 2001.

De las guías se extrajeron 30 recomendaciones, 53 incluyendo las sub-recomendaciones, que se dividieron en 10 secciones teniendo en cuenta las fases del proceso de consentimiento informado.

Se pidió a los expertos que calificaran la idoneidad de cada recomendación del 1 al 9, siendo 1 "extremadamente inapropiado" y 9 "extremadamente apropiado" (escala de idoneidad: 1 = "extremadamente inapropiado", 5 = "incierto", 9 = "extremadamente apropiado"). Se añadió la opción "No sabe", que debían utilizar únicamente cuando la pregunta se encontraba fuera del campo de experiencia del encuestado. La valoración la tenían que hacer teniendo en cuenta un participante potencial y un estudio clínico promedio, y debían centrarse en la eficacia de la recomendación sin tener en cuenta los costes. La encuesta la completaron en una plataforma electrónica. El proceso incluyó dos rondas de calificación y una reunión virtual que permitió presentar, aclarar y debatir los diferentes puntos de vista.

Keys to improving the informed consent process in research: Highlights of the i-CONSENT project (Anexo 5)

Este artículo editorial resume la metodología seguida en el Proyecto i-CONSENT y da a conocer las guías y las principales recomendaciones contenidas en ella.

Co-creation of information materials within the assent process: from theory to practice (Anexo 6)

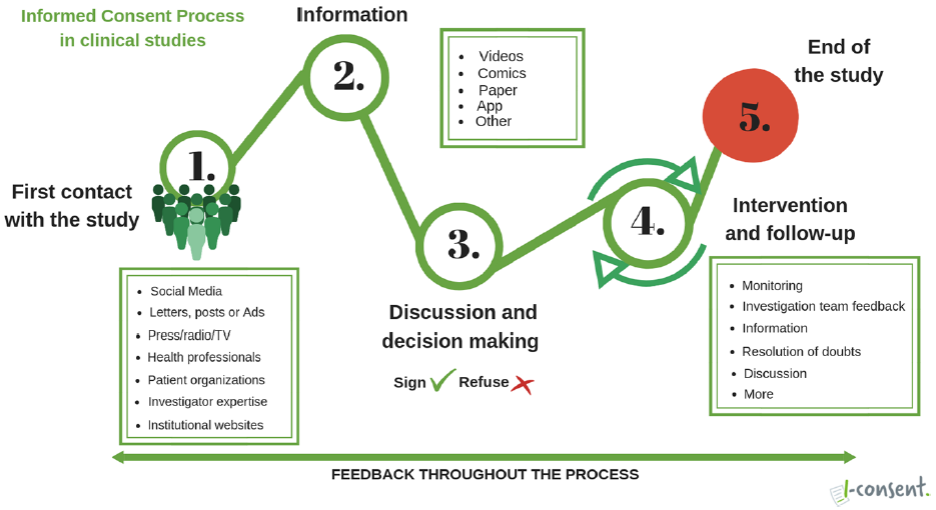
Este artículo explica el proceso de co-creación de unos materiales de asentimiento para un ensayo clínico hipotético con menores, siguiendo las recomendaciones contenidas en las “Guidelines for tailoring the Informed Consent Process in Clinical Studies”. Como parte central en este desarrollo de los materiales, se realizaron dos sesiones de “design thinking” con menores y sus padres/madres. Durante estas sesiones se exploraron las preferencias de los menores respecto al formato en el que recibir la información, se identificaron qué partes del texto no se entendían correctamente y se trabajaron junto a los/as menores unas definiciones de los términos más difíciles de comprender e ilustraciones relacionadas. También se co-diseñó con ellos/as una encuesta para medir la comprensión de los materiales realizadas a partir de la encuesta validada “Quality of Informed Consent” (QuIC).

RESULTADOS:

A partir de la evidencia científica previa y las investigaciones llevadas a cabo durante el proyecto se han elaborado unas recomendaciones para la mejora del consentimiento informado en investigación médica, de forma que este sea más compresivo para el potencial participante y se adecue mejor a sus necesidades y preferencias.

Además, se ha redefinido el consentimiento informado como un proceso, en 5 fases (ver figura 2), que comienza cuando el potencial participante recibe por primera vez información sobre el estudio y acaba al finalizar este, diferenciándose así de visiones más tradiciones y que se centran sobre todo en el acto puntual de la firma del consentimiento.

Figura 2. Fases del proceso de consentimiento informado



Fase 1. Primer contacto del potencial participante con el estudio:

Esta etapa tiene como objetivo dar a conocer el estudio y proporcionar la información esencial del mismo antes de que comience el proceso de reclutamiento. Desde el proyecto i-CONSENT recomendamos:

A. Considerar diferentes canales para el reclutamiento. Este primer contacto puede establecerse a través de diferentes canales como son: profesionales de la salud, redes de pacientes, sitios web institucionales o redes sociales. El acceso a los diferentes canales de comunicación varía según los distintos grupos de la sociedad, por lo que los canales de reclutamiento deben seleccionarse cuidadosamente, y siempre se debe tener en cuenta la idoneidad desde el punto de vista social, metodológico, legal y ético.

B. Utilizar mensajes de reclutamiento transparentes, equilibrados y neutrales. Deben incluir información objetiva en un lenguaje neutral. Deben ser claros y precisos. La información proporcionada durante este primer contacto debe permitir a los posibles participantes saber si están interesados en el estudio y si pueden participar (criterios de elegibilidad).
C. Revisar la estrategia de reclutamiento para garantizar que sea ética. Los comités de ética independientes correspondientes deben revisar y aprobar todos los materiales y métodos de reclutamiento, incluida la publicidad.

Fase 2- Suministro de información

Tras la manifestación inicial de interés, los posibles participantes deben recibir información adicional sobre la investigación. Ésta puede proporcionarse en formatos adaptados a las características o preferencias de los participantes potenciales. El suministro de información excesiva ("sobrecarga de información") puede suponer una información errónea y, por tanto, obstaculizar la calidad del proceso de consentimiento informado.

Desde el proyecto i-CONSENT recomendamos:

A. Proporcionar al participante toda la información pertinente sobre el estudio antes de la conversación con el investigador, asegurándose de que tenga tiempo suficiente para considerarla y para preparar las preguntas que pueda tener. Esta información debe entregarse de forma clara y concisa.
B. Considerar las nuevas tecnologías y formatos para entregar la información para complementar la discusión cara a cara. Se recomienda ofertar la información en más de un formato (papel, web, vídeo, infografías, cómic) e incluso combinarlos. Algunos de ellos facilitan el acceso remoto a la información y permiten que la información se entregue siempre de la misma manera, manteniendo una calidad constante.

Fase 3. Conversación y toma de decisiones

3.1 - Conversación

Una vez que se ha proporcionado la información al potencial participante y éste ha tenido tiempo de reflexionar sobre el contenido, los investigadores deben resolver las dudas sobre el estudio y la participación.

La conversación entre el potencial participante y el investigador debe garantizar que el potencial participante comprenda los aspectos relevantes relacionados con su participación.

Desde el proyecto i-CONSENT recomendamos:

A. Seleccionar un entorno adecuado para la conversación (que facilite el diálogo y garantice la privacidad).
B. Reforzar las habilidades de comunicación del investigador. No sólo importa "qué" se dice, sino también "cómo" y "por quién". Los investigadores pueden dirigirse a personas de distintos niveles educativos, culturales y sociales y deben hacerlo de manera eficaz, atenta y profesional para contribuir a que el potencial participante comprenda el estudio.
C. Comprobar la comprensión de los potenciales participantes. Es un elemento clave del proceso de consentimiento y depende del individuo (madurez, nivel educativo, etc.) y de la capacidad y voluntad de comunicación del investigador. El investigador debe asegurarse de que el potencial participante haya comprendido la información pertinente que le permita tomar una decisión informada y autónoma.

3.2 - Toma de decisiones

Si el potencial participante decide tomar parte en el estudio, tanto él como el investigador que ha dirigido la conversación deben firmar y fechar el formulario de consentimiento. En el caso de menores de edad, se requerirá el consentimiento de los padres o representantes legales y el asentimiento del menor de edad (cuando lo pueda proporcionar). Si durante su participación alcanza la mayoría de edad, deberá dar su consentimiento para continuar en la investigación.

Desde el proyecto i-CONSENT recomendamos:

A. Garantizar que los posibles participantes puedan tomar una decisión autónoma sobre su participación, sin ningún tipo de coacción, inducción indebida o engaño.
B. Utilizar ayudas a la decisión para facilitar el proceso de toma de decisiones
   Una ayuda para la toma de decisiones es una herramienta (por ejemplo, animaciones, materiales informativos interactivos o infografías) diseñada para realizar elecciones específicas y deliberativas entre varias opciones y posibles resultados presentados. Describe la decisión a tomar, las opciones disponibles y los posibles resultados de estas opciones (incluidos los beneficios, los daños y las incertidumbres) sobre la base de una cuidadosa revisión de las pruebas.

C. Proporcionar apoyo y dar el tiempo adecuado para que los participantes tomen una decisión u puedan consultar con otras personas antes de tomar una decisión final, si así lo desean.
D. Asegurarse de que los participantes conocen (y comprenden) toda la información del estudio y la posibilidad de retirarse en cualquier momento.

Fase 4- Intervención y seguimiento

Durante toda la duración del estudio, los participantes deben tener acceso a la información utilizada durante el proceso de reclutamiento y ser informados sobre cómo acceder a ella.

Si en algún momento del estudio hay cambios en el protocolo o se dispone de nuevos conocimientos relevantes, los participantes deben ser informados y deberán volver a dar su consentimiento (re-consentimiento). El nuevo consentimiento debe ser aprobado por el comité de ética.

Además de esto, i-CONSENT recomienda:

A. Asegurar que alguien del equipo investigador esté disponible para responder las preguntas o preocupaciones que los participantes puedan tener a lo largo del estudio.
B. Proporcionar a los participantes información actualizada sobre el estudio (desarrollo y el estado) a lo largo del mismo. Esta información puede proporcionarse telemáticamente para facilitar su acceso.

Fase 5- Finalización del estudio

Al finalizar el estudio, los participantes deben ser notificados e informados del tratamiento que se les asignó (si es el caso), así como de los resultados asociados, de acuerdo con la política de hallazgos incidentales acordada.

Toda la información sobre el tratamiento asignado, los procedimientos realizados y los resultados asociados deben quedar registrados en la historia clínica del participante. Si el participante expresa que no desea que se registren sus resultados, esto debe tenerse en cuenta.

Además de esto, desde el proyecto i-CONSENT recomendamos:

A. Agradecer a los participantes su participación mediante una carta de agradecimiento u otra forma de comunicación. Las cartas de agradecimiento son una buena oportunidad para destacar la importancia de la participación en la investigación y los objetivos que

cada participante ayudó a alcanzar. Debe incluir información sobre el estudio y un resumen de los resultados disponibles (o sobre cómo se podrá acceder a ellos una vez estén disponibles).

B. Incluir a los participantes en los primeros pasos de la difusión de resultados. Puede incluso incluir a participantes en diferentes actos de difusión dirigidos a ellos. Además debe proporcionarse un resumen de los resultados en lenguaje fácilmente comprensible.

Además, es recomendable *obtener la opinión de los participantes (feedback)* durante distintos momentos del proceso de consentimiento informado, como puede ser tras la fase de reclutamiento, durante la intervención o seguimiento y al finalizar su participación. El proyecto Transcelerate ha desarrollado unas encuestas para dicho fin[33]. Esta retroalimentación puede ayudar a definir y mejorar el proceso tanto para los estudios en curso como para los futuros, haciendo del consentimiento informado un proceso dinámico y adaptable.

Elaboración de ejemplos de materiales de consentimiento informado siguiendo las recomendaciones:

El proyecto además de elaborar las recomendaciones también las ha puesto en práctica, mediante la elaboración materiales de consentimiento dirigidos a distintas poblaciones (http://iconsent.pilotvalidation.eu/). Estos materiales se han diseñado y elaborado con la participación de representantes de la población objetivo (ver anexo 6). Adicionalmente se ha realizado un estudio que ha permitido medir la comprensión de estos materiales por representantes de la población objetivo y su satisfacción con estos (estudio no incluido en esta tesis), con resultados muy prometedores.

Las recomendaciones realizadas para mejorar los procesos de consentimiento informado han sido validadas por un grupo de expertos representativos de las principales partes interesadas: pacientes, investigadores, expertos en ética, miembros de comités de ética, industria farmacéutica y reguladores.

Uno de los artículos presentados en la tesis resume las principales aportaciones del proyecto y presenta las principales recomendaciones realizadas (Anexo 5).

PRESENTACIÓN DE LOS ARTÍCULOS

[33] Study Participant Feedback Questionnaire Toolkit [Internet]. TransCelerate Biopharma Inc. Disponible en: https://www.transceleratebiopharmainc.com/assets/patientexperience/study-participant-feedback-questionnaire/. [Citado 27 de octubre de 2022].

Revistas:

Las revistas seleccionadas para los artículos que componen esta tesis doctoral son 3:

- Rivista di BioDiritto – BioLaw Journal (ISSN 2284-4503) (artículos 1 y 2): es una revista en línea, de acceso abierto, cuyos artículos son revisados por pares y está indexada tanto en Web of Science - Emerging Sources Citation Index como en Scopus, entre otros. Esta revista interdisciplinar acoge contribuciones en los campos del derecho, las ciencias de la vida, la bioética y la inteligencia artificial. Desde 2018, la revista está incluida en la lista de calificaciones de revistas académicas "Clase A" en el campo de las ciencias jurídicas por la Agencia Nacional de Evaluación de Universidades e Institutos de Investigación de Italia. Además, Scimago Journal & Country Rank (SJR) consideraba dicha revista en el año 2019 (año de publicación de ambos artículos) como una revista de **segundo cuartil** tanto en la categoría "Law" como en "Philosophy"[34].
- BMC Medical Ethics (artículos 3 y 4). Es una revista on line, de acceso abierto, cuyos artículos son revisados por pares e indexada tanto en MEDLINE/PubMed como Scopus, entre otros. En ella se publican artículos originales de investigación relacionados con los aspectos éticos de la investigación biomédica y la práctica clínica. Scimago Journal & Country Rank (SJR) consideraba dicha revista en el año 2021 (año de publicación de ambos artículos) como una revista de **primer cuartil** tanto en la categoría "Health Policy" como en "Issues, Ethics and Legal Aspects" y en "Health (social science)"[35].
- Health Expectations (artículos 5 y 6). Es una revista on line, de acceso abierto, cuyos artículos son revisados por pares e indexada tanto en MEDLINE/PubMed como Scopus, entre otros. En ella se publican investigaciones originales, artículos de revisión y comentarios críticos. Health Expectations promueve el pensamiento crítico y el debate informado sobre todos los aspectos de la participación y el compromiso de los pacientes y el público en la atención sanitaria y social, la política sanitaria y los servicios de salud. Scimago Journal & Country Rank (SJR) consideraba dicha revista en el año 2021 (último dato disponible, el artículo incluido fue publicado en 2022) como

[34] BioLaw Journal. Scimago Journal & Country Rank (SJR). Scimago Lab. Disponible en: https://www.scimagojr.com/journalsearch.php?q=21100856416&tip=sid&clean=0. [Citado 27 de octubre de 2022]

[35] BMC Medical Ethics. Scimago Journal & Country Rank (SJR). Scimago Lab. Disponible en: https://www.scimagojr.com/journalsearch.php?q=28100&tip=sid&clean=0. [Citado 27 de octubre de 2022]

una revista de **primer cuartil** en la categoría "Public Health, Environmental and Occupational Health"[36].

Por tanto se considera que las 3 revistas seleccionadas son revistas de prestigio, cuyo impacto y calidad científica avalan el trabajo realizado y permiten darlo a conocer.

Artículos:

Dado que esta tesis es un compendio de 6 artículos, en este apartado de resultados se presentan los resúmenes de los mismos traducidos al castellano. Los textos completos de los artículos aparecen en la sección de anexos (Anexos 1 - 6).

i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process (Anexo 1)

El consentimiento informado es esencial para garantizar la autonomía de los participantes en la investigación clínica. Sin embargo, los documentos de consentimiento informado suelen ser complejos y difíciles de entender, y no incorporan la perspectiva de los pacientes. El proceso de consentimiento informado se ha centrado más en conseguir la firma del participante en el formulario de consentimiento informado, que en ser un contrato que garantice la autonomía del paciente mediante una información clara y completa sobre todos los aspectos relevantes de un ensayo. El proyecto i-CONSENT pretende mejorar la información que reciben los posibles participantes para tomar la decisión sobre su participación en un ensayo clínico, mediante el desarrollo de un conjunto de directrices para el proceso de consentimiento informado. Implicar a los posibles participantes durante la preparación del consentimiento informado y sus materiales asociados puede ser un factor clave.

Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements (Anexo 2)

Desde el punto de vista ético y jurídico, el consentimiento del menor para participar en una investigación médica es un tema de gran importancia. Todavía existe un debate sobre los requisitos para considerar este asentimiento como válido y vinculante. Esta revisión analiza y compara el contenido del asentimiento desde el punto de vista de la legislación y la literatura científica.

[36] Health Expectations. Scimago Journal & Country Rank (SJR). Scimago Lab. Disponible en: https://www.scimagojr.com/journalsearch.php?q=20885&tip=sid&clean=0. [Citado 28 de octubre de 2022]

Digital tools in the informed consent process: a systematic review (Anexo 3)

Antecedentes: Para alcanzar los objetivos del proceso de Consentimiento Informado es necesario proporcionar información comprensible a los pacientes, respetar y promover su autonomía y protegerlos de cualquier daño. En las últimas décadas, se han utilizado nuevas tecnologías, principalmente digitales, para aplicar y probar formatos innovadores en el proceso de Consentimiento Informado.

Se realizó una revisión sistemática para explorar el impacto del uso de herramientas digitales para el Consentimiento Informado tanto en la investigación clínica como en la práctica clínica. Se comparó la comprensión, la satisfacción y la participación del Proceso de Consentimiento Informado digital con el no digital.

Metodología: Se buscaron estudios en las bases de datos electrónicas disponibles, incluyendo Pubmed, EMBASE y Cochrane. Los estudios se identificaron utilizando términos/palabras clave específicos de Mesh. Se incluyeron estudios, publicados desde enero de 2012 hasta octubre de 2020, que se centraron en el uso de herramientas digitales de Consentimiento Informado para la investigación clínica o procedimientos clínicos. Las intervenciones digitales se definieron como intervenciones que utilizaron multimedia o audio/video para proporcionar información a los pacientes. Se clasificaron las intervenciones en 3 categorías diferentes: sólo vídeo, multimedia no interactivo y multimedia interactivo.

Resultados: La búsqueda arrojó 19.579 publicaciones. Tras el cribado de títulos y resúmenes, se retuvieron 100 estudios para el análisis del texto completo, de los cuales se incluyeron 73 publicaciones. Los estudios examinaron multimedia interactivos (29/73), multimedia no interactivos (13/73) y vídeos (31/73), y la mayoría (34/38) de los estudios se realizaron en adultos. Las innovaciones en el consentimiento se probaron para procedimientos clínicos/quirúrgicos (26/38) y para la investigación clínica (12/38). En el caso de la investigación sobre Consentimiento Informado, se exploraron 21 resultados, observándose un efecto positivo en al menos uno de los resultados estudiados en 8/12 estudios. Para los procedimientos clínicos/quirúrgicos se exploraron 49 resultados, y 21/26 estudios informaron de un efecto positivo en al menos uno de los resultados estudiados.

Conclusiones: Los artículos no mostraron que las tecnologías digitales para el consentimiento informado afectaran negativamente a ninguno de los resultados y, en general, las herramientas multimedia parecen deseables. Las herramientas multimedia indicaron un mayor impacto que los solo los vídeos. La presencia de un investigador puede mejorar

potencialmente los resultados en las investigaciones sobre los procesos de Consentimiento Informado. El diseño de los estudios fue heterogéneo, lo que dificulta la evaluación del impacto. Se necesita un diseño de estudio sólido que incluya la estandarización para evaluar el impacto de forma concluyente.

Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies (Anexo 4)

Antecedentes: El proyecto i-CONSENT de H2020 ha desarrollado un conjunto de directrices que ofrecen recomendaciones éticas y herramientas prácticas destinadas a hacer que el proceso de consentimiento informado en los estudios clínicos sea más completo, adaptado e inclusivo. Un grupo de expertos que representa a distintas partes interesadas ha analizado la idoneidad de algunas de sus novedosas recomendaciones.

Métodos: Se utilizó una adaptación del Método de Adecuación RAND/UCLA para evaluar el nivel de acuerdo sobre las recomendaciones por parte de 14 representantes de diferentes partes interesadas, incluyendo pacientes, reguladores, investigadores, expertos en ética y la industria farmacéutica. El proceso incluyó dos rondas de calificación y una reunión virtual.

Resultados: Se evaluaron 53 recomendaciones. Tras la primera ronda, 34 recomendaciones se consideraron "apropiadas"; 19 se consideraron "inciertas"; y ninguna se consideró "inapropiada". Tras la segunda ronda, 9 "inciertas" cambiaron a "apropiadas". Todas las recomendaciones obtuvieron medianas entre 6,5 y 9 en una escala de 1 a 9 (1 = "extremadamente inapropiado", 5 = "incierto", 9 = "extremadamente apropiado"). Las secciones "Recomendaciones generales" y "Perspectiva de género durante el proceso de consentimiento para estudios clínicos" mostraron la mayor cantidad de recomendaciones con la calificación "incierto". Las cuatro claves para mejorar la comprensión del PCI en los estudios clínicos son (1) considerar el consentimiento como una interacción continua bidireccional que comienza en el primer contacto con el potencial participante y continúa hasta el final del estudio; (2) mejorar las habilidades de comunicación de los investigadores; (3) co-crear la información; y (4) utilizar un enfoque por capas, incluyendo información para compensar la posible falta de conocimientos de salud del potencial participante y un glosario de términos.

Conclusiones: El método RAND/UCLA ha demostrado su validez para evaluar la idoneidad de las recomendaciones de las directrices éticas. Las recomendaciones de las directrices de i-CONSENT fueron consideradas en su mayoría "apropiadas" por todas las partes implicadas en el proceso de consentimiento informado.

Keys to improving the informed consent process in research: Highlights of the i-CONSENT project (Anexo 5).[37]

La gestión ética y jurídica de todos los aspectos del consentimiento informado en investigación es cada vez más amplia y compleja. En lugar de regirse por una directiva única, el consentimiento informado se rige por una serie de normas aplicadas a la investigación biomédica, los ensayos clínicos y los biobancos publicadas por diferentes organismos internacionales.

El consentimiento informado es una parte esencial de cualquier investigación con seres humanos, pero la variedad de directrices disponibles puede complicar el proceso de consentimiento informado para los patrocinadores, los investigadores y los participantes.

Los patrocinadores, en particular, tienen dificultades para adaptar el proceso de consentimiento informado a las características de los participantes. Además, debido a la longitud y la complejidad de los consentimientos informados, algunos participantes pueden malinterpretar puntos clave y aceptar participar en un ensayo que no comprenden del todo. En estos casos, la decisión sobre su participación se basa principalmente en la conversación con el investigador, lo que carece de trazabilidad.

En 2017, la Comisión Europea respondió a la necesidad de mejorar el proceso de consentimiento informado y la legibilidad del mismo poniendo en marcha el proyecto 'Mejora de las directrices del consentimiento informado, incluyendo a las poblaciones vulnerables, bajo una perspectiva de género (i-CONSENT)' (Acuerdo de subvención 741856).

El marco ético y jurídico del proyecto i-CONSENT se complementó posteriormente con la publicación "Guidelines for Tailoring the Informed Consent Process in Clinical Studies" (Directrices para adaptar el proceso de consentimiento informado en los estudios clínicos), que incluye directrices más específicas para elaborar materiales de información al paciente basados en pruebas que tengan en cuenta el género, el multiculturalismo y las poblaciones vulnerables, que suelen estar infrarrepresentadas en la investigación. Las directrices también ofrecen una serie de hojas informativas y herramientas de fácil lectura y uso que complementan el documento principal, destacan la importancia de diversos aspectos del proceso de consentimiento informado y ofrecen recomendaciones sobre cómo aplicar las mejores prácticas. Estas hojas informativas incluyen, entre otras cosas, cómo presentar la

[37] Dado que por el formato de artículo este carece de resumen en este caso se ha incluido la introducción del artículo, que resume su contenido

información del estudio en los materiales de consentimiento; cómo evaluar la comprensión de los participantes; cómo establecer una relación adecuada entre el investigador y el participante durante el proceso; y cómo abordar algunos de los principales desafíos éticos que pueden surgir en situaciones de pandemia, como la de COVID-19.

Este artículo resume los aspectos clave del proceso de consentimiento informado desde la perspectiva del proyecto i-CONSENT.

Durante la elaboración de las directrices, se llevaron a cabo múltiples revisiones de la literatura científica y de los textos éticos y legales, así como talleres, seminarios y encuestas que nos permitieron obtener las opiniones sobre distintos aspectos del consentimiento informado de diferentes personas, entre ellas representantes de pacientes y potenciales participantes en estudios clínicos, expertos en legislación, expertos en ética, miembros de comités de ética, investigadores, miembros de la industria farmacéutica, legisladores y mediadores culturales.

Las directrices mencionadas y el resto de los productos del proyecto del proyecto se pueden consultar en la plataforma CORDIS.

Co-creation of information materials within the assent process: from theory to practice (Anexo 6)

Introducción: El proceso de consentimiento informado es clave para salvaguardar la autonomía del participante en la investigación médica. Para que este proceso sea válido, la información presentada al potencial participante debe satisfacer sus necesidades y ser comprendida por él. El proyecto i-CONSENT ha elaborado las “"Guidelines for Tailoring the Informed Consent Process in Clinical Studies" (Directrices para adaptar el proceso de consentimiento informado en los estudios clínicos), cuyo objetivo es mejorar los procedimientos de consentimiento informado para que sean más fáciles de entender y se adapten mejor a las necesidades y preferencias de la población a la que van dirigidos. La mejor manera de adaptar la información a las características y preferencias de la población destinataria es implicar a la propia comunidad.

Métodos: Siguiendo las directrices desarrolladas por i-CONSENT, se co-crearon materiales de asentimiento para un ensayo clínico simulado de la vacuna contra el virus del papiloma humano (VPH) en adolescentes. Durante el proceso, se llevaron a cabo dos sesiones de design thinking en las que participaron un total de 10 niños y 5 padres. Los objetivos de las sesiones eran: conocer la opinión de los niños sobre el proceso de consentimiento informado (asentimiento en su caso) en los ensayos clínicos; identificar las partes más difíciles de

entender y las alternativas para su presentación y redacción; identificar los formatos preferidos para recibir la información y las principales características de estos formatos, diseñar un vídeo explicativo del ensayo clínico y evaluar una herramienta de evaluación de la comprensión.

Resultados: Se co-crearon materiales de asentimiento en 3 formatos: un material web siguiendo un enfoque por capas; un vídeo en formato de historia; un documento pdf con una forma innovadora de presentar la información en comparación con los documentos de asentimiento tradicionales. Además, se co-diseñó el Cuestionario de Comprensión del Asentimiento (C-CAsIn), basado en el cuestionario de Calidad del Consentimiento Informado (QuIC).

Conclusión: La metodología de design thinking ha demostrado ser una herramienta fácil y útil para involucrar a los niños en el diseño de información adaptada a sus necesidades y preferencias.

Contribución del paciente o del público: Una muestra de la población objetivo participó en el diseño y el pilotaje de los materiales creados con la metodología del design thinking. Además, los representantes de los pacientes participaron en el diseño y la evaluación de las directrices desarrolladas por el proyecto i-CONSENT que se siguieron para la elaboración de los materiales de este estudio.

CONCLUSIONES

El consentimiento informado en investigación sigue teniendo mucho margen de mejora y se debe de hacer un esfuerzo por cambiar el concepto actual que muchos investigadores, patrocinadores y potenciales participantes tienen sobre él.

Es importante entender la mejora del consentimiento informado como un cambio de paradigma, en el que el consentimiento informado lejos de ser un acto puntual y un requisito burocrático, es un proceso de comunicación continuo bidireccional que va desde el primer contacto del potencial participante con la investigación hasta que acaba su participación en esta. Además, este proceso puede tener un gran valor añadido, ya que puede ser aprovechado para mejorar los conocimientos en salud y sobre investigación de la población y contrarrestar algunas de las noticias falsas y los bulos tan extendidos en la actualidad y los peligrosos que conllevan.

Una de las claves fundamentales para que el consentimiento informado se comprenda y se adapte a las necesidades de los potenciales participantes es conocer a tu población objetivo, ya que en muchos casos no coincide la información que se considera relevante por parte de los distintos actores (legisladores, miembros de comités de ética, patrocinadores, investigadores, participantes). Por lo que es importante asegurarnos que la información que les facilitamos, además de cumplir con los requisitos legales y éticos, responde a sus necesidades.

Para conocer a nuestra población objetivo, se pueden realizar diversas aproximaciones, como son la revisión de la literatura, entrevistas con informantes clave, análisis de los mensajes en redes sociales, encuestas a la población objetivo… Sin embargo, se considera especialmente efectivo incluir metodologías que involucren directamente a la población objetivo en el diseño y revisión de los materiales de consentimiento, co-creándolos con ellos, por ejemplo mediante la técnica de design thinking.

La inclusión de las herramientas digitales en el consentimiento informado y el desarrollo con ello de los consentimientos informados electrónicos es una de las principales líneas de investigación actuales respecto al consentimiento informado. Diversos estudios han intentado evaluar el impacto del uso de la tecnología y de las herramientas multimedia en la comprensión y retención de la información y en la satisfacción de los potenciales participantes con la información facilitada. Los resultados de dichos estudios respecto a la comprensión de la información son prometedores, aunque no son concluyentes. Aun así, respecto a lo que sí hay consenso, es que no son perjudiciales. Además, los resultados muestran que el uso de las herramientas multimedia en general mejora la satisfacción de los potenciales participantes y la retención de la información. El impacto de las herramientas multimedia es más positivo si estas herramientas son interactivas.

Además, en el caso de los consentimientos informados electrónicos, se considera especialmente recomendable la presentación de la información por capas, incluyendo en una primera capa la información esencial y obligatoria por ley y, en capas sucesivas, información adicional que permita al potencial participante profundizar sobre aquellos aspectos que le resulten de mayor interés o sobre los que necesite mayor información. La inclusión de un glosario de términos (en lenguaje sencillo y, a ser posible, acompañado de ilustraciones) también es una gran ayuda para mejorar la comprensión y la alfabetización en salud.

Es importante indicar que es muy positivo ofrecer al participante más de una opción para recibir la información como puede ser, además del consentimiento informado por página web, el documento (preferiblemente mejorado y en un enfoque también por capas utilizado, en

lugar de hipervínculos, anexos o cajas de texto en distintos colores) u otros formatos como pueden ser vídeo o cómic, y el uso de infografías. En la página web http://iconsent.pilotvalidation.eu/ se pueden encontrar ejemplos de consentimientos informados que ofertan la información en distintos formatos (web, documento y vídeo), y que han sido realizados siguiendo las recomendaciones contenidas en las "Directrices para adaptar el proceso de consentimiento informado en los estudios clínicos", incluyendo el proceso de co-creación, tal y como se muestra en el artículo 6 presentado en la presente tesis.

Además de los aspectos ya mencionados, en la evaluación de la idoneidad de las principales recomendaciones contenidas en las "Directrices para adaptar el proceso de consentimiento informado en los estudios clínicos" por expertos representativos de las principales partes interesadas, se destacó la importancia de entender el consentimiento informado como ese proceso comunicativo bidireccional continuo, ya mencionado anteriormente, y se enfatizó la importancia de que el personal investigador tenga las habilidades y formación necesaria para poder realizar de forma adecuada esta comunicación, incluyendo llevar a cabo mediante una conversación natural la verificación de la comprensión de la información por parte del potencial participante, evitando así el uso de técnicas y herramientas que puedan resultar artificiales y hacer sentir examinado al potencial participante.

Para finalizar, quiero indicar que las directrices elaboradas durante el proyecto i-CONSENT pueden ser de gran utilidad para iniciar el cambio de paradigma y mentalidad respecto a la forma de conceptualizar el consentimiento informado. Contienen recomendaciones prácticas sobre diversos aspectos de la investigación biomédica que pueden complementar las guías, directrices y legislación actual.

Estrategia para la implementación de las recomendaciones

Es importante señalar que las recomendaciones contenidas en las guías de i-CONSENT y en esta tesis no tienen que verse como un todo o un nada, sino como una herramienta que permite guiar sobre distintos aspectos y que el/la investigador/a debe adaptar a sus necesidades y su realidad (incluyendo sus limitaciones). De hecho, esta tesis y el proyecto i-CONSENT pretenden evidenciar la necesidad de cambio, que otra forma de hacer el consentimiento informado es posible y servir de guía para este.

Pese a que las recomendaciones incluidas en la guía se basan en la evidencia científica y existen proyectos en la misma temática (incluyendo la iniciativa Transcelerate BioPharma) que apoyan también un cambio en el proceso de consentimiento informado y la dirección de este,

sigue existiendo una cierta resistencia a implementarlo en este momento. La mayor inversión en tiempo y dinero que exige, la falta de literatura científica concluyente respecto a los beneficios en la comprensión de la incorporación de elementos multimedia (sí que existe en el incremento de la satisfacción) o la consideración por parte de algunos investigadores y patrocinadores del consentimiento informado como un acto burocrático o ritualista más que como un valor añadido, son algunos de los motivos que están frenando este cambio necesario.

Así pues, entiendo que la estrategia fundamental a seguir en este momento es la continuar sensibilizando, formando y trabajando en la diseminación de las ideas que fundamentan estas guías, intentando contribuir a este cambio. Es importante señalar que en esta ardua tarea no estamos solos, sino que nos encontramos en un momento histórico en el que está dando importancia a aspectos de la investigación como la incorporación ciudadana en el diseño de la investigación y en la co-creación de los materiales destinados a ellos, la mejora de la autonomía de los participantes, la equidad, el retorno de resultados a los participantes, el fomento de actividades remotas y que se está intentando cambiar el foco de una investigación centrada en el patrocinador y el investigador a una investigación centrada en el participante. Cada vez hay más proyectos internacionales, tanto públicos como privados que trabajan en esta dirección y es importante intentar participar o contactar con ellos para poder trasladar a ellos el conocimiento adquirido en esta tesis y este proyecto.

Actualmente se está participando en las iniciativas que trabajan la temática del consentimiento informado (como es el grupo de trabajo sobre Consentimiento Informado Electrónico e Inclusión del Foro Europeo de Buenas Prácticas Clínicas) o de la digitalización en los procesos de investigación (como el proyecto europeo Trials@Home), se están explicando las guías, la importancia del cambio y mostrando los materiales de ejemplo realizados en distintos foros especializados, como son los congresos profesionales o las iniciativas de la industria farmacéutica y por supuesto escribiendo artículos en especializados.

Pero, además de lo que se puede hacer a título individual o desde las entidades que han participado en el proyecto i-CONSENT, hay varios actores que pueden desempeñar un papel relevante fomentando este cambio de mentalidad e impulsando la implementación de estas recomendaciones, por lo que es importante intentar incluirlos en las actividades de diseminación e implementación. Entre ellos se encuentran:

- La Comisión Europea (financiadora del proyecto): es quien identificó en primera estancia la necesidad de este cambio y puede impulsar su implementación introduciéndola como parte de sus guías éticas en los proyectos que financie.

- La industria farmacéutica: lleva años interesada en desarrollar el consentimiento electrónico. La iniciativa Transcelerate BioPharma desarrolló unas guías a este respecto, así como unas pautas para conocer la satisfacción del participante sobre el proceso de consentimiento. Ambos aspectos reflejan parte de las recomendaciones del proyecto. Asimismo, miembros de esta industria participan en múltiples proyectos internacionales encaminados a dar una mayor relevancia al participante en los procesos de la investigación, ya que sin participantes no hay estudio. Un cambio de mentalidad en este sector, que vea el consentimiento informado como una inversión (en satisfacción e información al participante que le haga confiar en la investigación y evite abandonos) y un valor añadido, y no como un acto burocrático y un coste fomentaría mucho la implementación de las recomendaciones recogidas en esta guía.

- Comunidad científica: La escasez de herramientas validadas que permitan medir de una forma adecuada la comprensión del consentimiento informado hacen que falte literatura científica concluyente respecto a los beneficios del uso de diversos formatos y herramientas digitales respecto a la comprensión de la información y la satisfacción de los potenciales participantes. Un mayor número de estudios utilizando herramientas validadas y homogéneas permitirían comparar los distintos formatos y mejoras introducidos en los procesos de consentimiento informado e identificar las mejores prácticas.

- Comités de ética en investigación: Son en última estancia quienes aprueban o rechazan los procedimientos descritos en los protocolos de estudio, asimismo revisan y dan el visto bueno a los materiales y procedimientos descritos respecto al consentimiento informado, pudiendo aceptar o rechazar la puesta en práctica de las recomendaciones descritas en esta tesis y en las guías del proyecto i-CONSENT. La importancia que den al proceso de consentimiento informado y lo críticos que se muestren con los materiales de información utilizados en este proceso puede ser fundamental para impulsar la implementación de estas guías. Comprendo que también tienen que valorar la factibilidad de la aplicación de estas recomendaciones y no solo su conveniencia.

- Agencias reguladoras: fundamentales no solo en potenciar el uso de estas recomendaciones, sino también en aceptar los cambios que aquí se proponen. La aceptación del consentimiento electrónico, es un ejemplo de esto.

- Equipos investigadores: Son una parte fundamental en el proceso de consentimiento informado. La importancia que den al proceso de consentimiento informado en sí, a informar correctamente, a la comunicación con el participante, a la comprobación de que la

comprensión ha sido adecuada y la habilidad que tenga para hacer todo esto son fundamentales para que el proceso de consentimiento informado resulte exitoso.

Es importante señalar que miembros representativos de todos estos grupos (además de representantes de los potenciales participantes) han participado en algún momento en el desarrollo y evaluación de las recomendaciones incluidas en las guías.

PRINCIPALES APRENDIZAJES DESDE LA COORDINACIÓN DE UN PROJECTO EUROPEO

Además del producto científico aquí presentado, uno de los grandes aprendizajes obtenidos durante esta tesis doctoral ha sido la participación como coordinador científico del proyecto europeo en el que esta se enmarca, el proyecto i-CONSENT.

Se debe tener en cuenta que gran parte de la investigación en nuestro país se hace a partir de fondos obtenidos en convocatorias competitivas, dentro de las cuales las convocatorias europeas tienen especial importancia. Todos los procesos que conllevan estos proyectos, desde la búsqueda de socios, la redacción de propuestas, negociación de los roles y presupuestos, las relación y comunicación con los socios y con los representantes de la Comisión Europea, la redacción de enmiendas, la justificación del proyecto (técnica y financieramente), la defensa de este frente a la Comisión Europea, etc., han sido un aprendizaje extremadamente valioso para mí y considero que puede serlo para cualquier investigador.

Además, en este proyecto nos encontramos varios retos que como coordinadores que hicieron que este proceso fuese aún más enriquecedor, como fueron:

- Bancarrota del socio que se encargaba del paquete de comunicación del proyecto. Era una empresa muy joven, con una propuesta atractiva y práctica, muy orientada a los proyectos europeos. Logró una gran éxito, participando en 6 proyectos europeos y siendo reconocida en los Premios Europeos a la Excelencia (nominada al premio en la categoría "Nueva agencia del año 2016" y ganadora al premio en la categoría "Consultoría del año 2017”). Este éxito les llevó a un rápido crecimiento, que no supieron gestionar y que acabó con su cierre por bancarrota durante el primer semestre de 2018. Esta situación fue un importante revés para el consorcio, teniendo FISABIO que asumir las tareas de dicha entidad en el proyecto, incluyendo la coordinación del paquete de trabajo de comunicación, para lo que incorporó a una periodista al equipo de trabajo. Afortunadamente, el coordinador del proyecto

(FISABIO) planificó las transferencias a los socios de una forma fraccionada, con una transferencia inicial y transferencias posteriores tras la consecución de ciertos hitos y la justificación de un porcentaje de gasto. Esta forma de gestión permitió un menor impacto económico de esta situación al proyecto.

- El Brexit: en el consorcio había 2 socios con sede social en Reino Unido, uno de ellos decidió cerrar su empresa en dicho país y abrir otra nueva en Bélgica, transfiriendo sus funciones en el consorcio de la una a la otra. El traslado del socio conllevo una ligera demora en algunas actividades, debido a los procesos propios del cierre de una empresa y apertura de la otra, y al traslado físico del socio a Bruselas. El Brexit también tuvo impacto en el diseño de algunas actividades por la transferencia de datos con un país de fuera de la Unión Europea.
- La entrada en vigor de una nueva regulación de protección de datos: Esta tuvo impacto tanto en la temática de la investigación (aspectos legales del consentimiento informado), como en la gestión de la gestión de los datos del consorcio. Estos cambios se tuvieron que reflejar en el Plan de Gestión de Datos y en los entregables de ética del proyecto.
- La oportunidad de aplicar los resultados de la investigación en un entorno real: Durante el proyecto surgió la posibilidad de aplicar las recomendaciones a la elaboración de los materiales de consentimiento de un ensayo clínico real (https://estudiovigira.es/) y probar su uso en dicho entorno real. Esto llevó a la solicitud de una ampliación en la extensión del proyecto (en la que se incluyó también el estudio de la evaluación de la idoneidad de las recomendaciones por parte de expertos). El personal de unidad de Ethics and Research Integrity (ERI) de la Comisión Europea identificó como una posibilidad única el probar las guías en un ensayo clínico real y apoyó de forma enérgica la realización de las dos nuevas validaciones (expertos y ensayo clínico real). Esta situación derivó en la ampliación del proyecto durante 11 meses.
- El proyecto i-CONSENT participó en el "Open Research Data Pilot". La participación en este piloto de la Comisión Europea conllevó la necesidad de desarrollar el Data Management Plan (DPM) y publicar, en la medida de lo posible, no solo los artículos sino también los datos de la investigación en abierto. Dado lo novedoso de esta iniciativa y las escasas experiencias disponibles sobre el diseño y elaboración de DMP, la tarea resultó bastante compleja y enriquecedora. La falta de ejemplos de proyectos anteriores a los que acudir, llevo a la necesidad de "interpretar desde cero" las indicaciones de la Comisión Europea, establecer protocolos de actuación y modelos de

gestión de datos que luego han servido como ejemplo para otros proyectos. Además, tuvimos que familiarizarnos con la terminología y los conceptos del "FAIR Data Management" y aprender a identificar y utilizar los repositorios que permitiesen cumplir con los compromisos con la Comisión Europea en esta temática.

- La COVID-19, lógicamente la situación de pandemia tuvo un gran impacto en el día a día del proyecto:
    - Modificó la forma de relacionarse y comunicarse tanto entre los socios (al suprimir reuniones presenciales) como interna en FISABIO (por adoptar el teletrabajo como forma de trabajo diaria, suprimiendo las reuniones presenciales y el contacto personal diario).
    - La diseminación de los resultados del proyecto se había basado hasta ese momento en la participación en congresos, que pasaron primero a retrasarse o incluso a cancelarse y posteriormente a adaptarse al formato en línea. Esto provocó que la difusión de resultados en congresos disminuyese mucho durante el último año de proyecto. Además, el evento final del proyecto tuvo que adaptarse a la situación epidemiológica y hacerse de forma virtual, modificando su estructura y la forma de diseminarlo.
    - Adaptaciones metodológicas. La situación epidemiológica tuvo un gran impacto en varias actividades científicas del proyecto, tanto en reuniones con expertos como, sobre todo, en los estudios de validación. La forma de reclutar participantes se tuvo que modificar, las encuestas pasaron a realizarse en línea, la sesión presencial del estudio de validación con expertos se tuvo que hacer por teleconferencia, la co-creación de los materiales de consentimiento para el ensayo clínico Vigira cambió por entrevistas individuales y encuestas en línea; el proceso de consentimiento informado de dichos estudios modificaron incorporando procedimientos remotos…
    - Inclusión de recomendaciones sobre situaciones de pandemia. Aunque inicialmente no estaba previsto realizar recomendaciones sobre esta temática, la actualidad hizo que las guías ampliasen su contenido para abarcar esta temática, lo que llevó a realizar investigaciones al respecto. Además, el proyecto i-CONSENT se encargó de coordinar y participar en la elaboración del monográfico de la revista científica Biolaw Journal "i-CONSENT – Informed consent in clinical trial in the context of the Covid-19 pandemic. Ethical and legal challenges".

- El formato de algunos entregables: Algunos entregables se incluyeron en la propuestas como artículos científicos, la experiencia ha demostrado que esto fue un error, dado que los procesos de revisión de algunas revistas son mucho más largos de lo esperado y ponen en serio riesgo la presentación del entregable, asimismo no se puede asegurar que el artículo vaya a ser aceptado, por ello se recomienda comprometerse al envío del artículo a la revista más que a la publicación de este.
- Personal implicado en el proyecto, durante el proyecto se vivieron distintas situaciones:
    - La implicación de los socios puede variar mucho a lo largo del proyecto en función de su rol en cada momento (por ejemplo si se encuentran liderando o no una tarea en ese momento), por eso se recomienda tener esto en cuenta durante la fase de propuesta y hacer una distribución adecuada y estratégica (puede ser mejor tener pocos socios muy implicados, que muchos con poca participación).
    - Por otro lado se vio como las contrataciones en algunos momentos se demoraban más de lo esperado por las dificultades de encontrar personal con el perfil requerido y las condiciones ofrecidas (contratos ligados a la duración de las actividades de dicho socio en el proyecto).
    - Fuga de personal del proyecto. La duración de los contratos ligada a las actividades del socio en el proyecto hace que se den situaciones de discontinuidad de algunos investigadores o que acaben su contrato cuando la implicación del socio disminuye, lo que dificulta la transferencia de resultados, o que cambien de trabajo durante el proyecto. Esto puede provocar problemas en la transferencia de conocimientos, pero también de distribución de cargas de trabajo entre los investigadores que quedan en el consorcio, que en muchos casos deben asumir las tareas que estaba realizando la persona que se ha ido, por las dificultades de encontrar una persona nueva que la sustituya, poniendo en algunos en riesgo los tiempos o la calidad de los entregables.

Todas estas vivencias, unidos a las experiencias habituales de un proyecto europeo (trabajar con personas de distintos países y culturas, trabajar de forma descentralizada, utilizar el inglés como lengua de comunicación predominante en el trabajo diario, organizar y participar en reuniones y eventos, representar al consorcio en congresos y reuniones, defender el proyecto

frente al personal de la Comisión Europea) han constituido un aprendizaje continuo y muy gratificante.

CONTINUIDAD DE LA LÍNEA DE INVESTIGACIÓN

La línea sobre ética de investigación iniciada con el proyecto i-CONSENT y la presente tesis no finaliza con ellos. Gracias a la experiencia y conocimientos obtenidos durante estos años, estoy participando como investigador en el proyecto europeo Trials@Home (H2020- JTI- IMI2, acuerdo de consorcio nº 831458), del que FISABIO es socio, el cual tiene como objetivo remodelar el diseño, la realización y las operaciones de los ensayos clínicos, mediante el desarrollo y la puesta a prueba de normas, recomendaciones y herramientas para la definición y puesta en marcha de ensayos clínicos descentralizados (ECD) en Europa. Dentro de este proyecto, que finaliza en 2024, estoy participando especialmente en los temas referentes al consentimiento informado, la implicación y reclutamiento de participantes y los aspectos éticos y legales de los ECD.

Además, he participado durante el año 2021 como investigador en el proyecto de investigación "Estratègies de millora de la informació i la comunicació sanitàries encontextos multilingües i multiculturals" de la convocatoria UJISABIO (donde trabajan de forma conjunta equipos de investigación de la Universitat Jaume I y FISABIO). Este proyecto de duración anual se centró en conocer las necesidades y preferencias de investigadores y potenciales participantes en ensayos clínicos respecto al consentimiento informado, con el fin de diseñar una aplicación que guíe al investigador en la elaboración de los consentimientos informados para ensayos clínicos. Al corresponder esta convocatoria a una acción preparatoria su fin es poder presentar en el futuro una propuesta de investigación a otra convocatoria para continuar dicha investigación y llevar a cabo esa idea.

Asimismo, en la actualidad estoy trabajando con la Red Valenciana de Biobancos y el área de investigación en cáncer y salud pública de FISABIO para el diseño de unos consentimientos informados digitales y del portal del donante (e-donante). Una propuesta de desarrollo de dicho portal se ha presentado a las XXIVª Convocatoria de Becas sobre Bioética 2022 de la Fundació Víctor Grífols i Lucas, habiendo resultado premiada, lo que ha permitido lograr financiación para realizar su prueba de concepto (TRL3) así como su validación en entorno de laboratorio (TRL4). Una vez se obtenga el grado de desarrollo TRL4, se presentará el portal a las convocatorias de ayudas de innovación que permitan desarrollarlo plenamente.

Por otro lado he sido invitado y estoy participando en actividades del grupo de trabajo sobre Consentimiento Informado Electrónico e Inclusión del Foro Europeo de Buenas Prácticas Clínicas, una iniciativa muy potente que pretende continuar definiendo estos aspectos y su uso en los ensayos clínicos.

De este modo, y con las nuevas oportunidades que vayan surgiendo, espero seguir trabajando durante los próximos años en esta línea de investigación iniciada con el proyecto i-CONSENT y esta tesis doctoral.

ANEXO 1: i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process

Special issue

i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process

Jaime Fons-Martínez, Cristina Ferrer-Albero, Rosanna Russell, Elizabeth Rodgers, Linda Glennie, Javier Díez-Domingo*

ABSTRACT: Informed consent is essential in ensuring the autonomy of participants in clinical research. However, informed consent documents are often complex and difficult to understand, and do not incorporate the patients' perspective. The informed consent process has become more focused on acquiring the participant's signature on the informed consent form, rather than being a contract that ensures the patient's autonomy through clear and complete information about all relevant aspects of a trial. The i-CONSENT project aims to improve the information that potential participants receive when deciding whether or not to join a clinical trial through the development of a set of guidelines for the informed consent process. Involving potential participants during the preparation of the informed consent and its associated materials can be a key factor.

KEYWORDS: Bioethics; clinical research; hard law; informed consent; patient participation

SUMMARY: 1. The development of informed consent – 2. The need for changes to the informed consent process – 3. Participants' opinion of the informed consent – 4. Conclusion.

* *Jaime Fons-Martínez: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: fons_jai@gva.es; Cristina Ferrer-Albero: Facultad de Enfermería. Universidad Católica Valencia San Vicente Mártir (UCV). Valencia. E-mail: cristina.ferrer@ucv.es; Rossana Russell: Meningitis Research Foundation. United Kingdom. E-mail: rosannar@meningitis.org; Elizabeth Rodgers: Meningitis Research Foundation. United Kingdom. E-mail: Elizabethr@meningitis.org; Linda Glennie: Meningitis Research Foundation. United Kingdom. E-mail: lindag@meningitis.org; Javier Díez-Domingo: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: jdiezdomingo@gmail.com.* *The article was subject to a double-blind peer review process.*
This essay is developed within the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), funded by the European Union framework program H2020 (Grant Agreement n. 741856).

ISSN 2284-4503

1. The development of informed consent

Since the publication of the Belmont Report[1], the principle of autonomy for individuals participating in research has become a key consideration. The report highlighted the importance of informed and voluntary consent by stating that participants should be treated as autonomous entities and that those with diminished autonomy should be protected.

The Report acknowledges that the informed consent process contains three main components: information, comprehension and voluntariness. Fulfilling each of these components can however present challenges. For example, with regards to the information, for some research, complete disclosure may jeopardize the validity of the project; such as in double blind controlled trials, where neither the participant nor investigator is informed of who is receiving a particular intervention, in order to avoid study bias. Withholding such information is deemed acceptable, as long as participants are aware that some aspects of the research are not able to be revealed until the study has concluded, and that incomplete disclosure is indeed an essential requirement to fulfil study objectives, and not just a convenience factor. For the comprehension element, it is suggested that a person's capacity to understand depends on a multitude of factors including intelligence, reasoning, maturity and language. Moreover, the way in which information is presented, is considered to be as important as the content itself in enabling an individual to make an informed decision.

Participants with limited comprehension require special consideration. However, where possible these individuals should still be given the opportunity to decide whether or not to take part in research, except for when the research provides a therapy which would be otherwise unavailable: "the objections of these subjects to involvement should be honoured, unless the research entails providing them a therapy unavailable elsewhere". The Report proposes that in such cases information should also be given to a third party who is more likely to understand the potential participants' situation and is able to act in their best interest.

When the Belmont Report was published, the supervision of the principle of autonomy by independent committees, now known as ethics committees, was not required. These independent committees were however acknowledged to have an important role in assessing beneficence, and any potential risks and benefits associated with the investigation.

Informed consent is also referenced within the Declaration of Helsinki by the World Medical Association (WMA) and Guidelines for Good Clinical Practice by the International Conference on Harmonisation (ICH).

The last revision of the Declaration of Helsinki[2] mentions, in point 26, that in medical research, each potential participant must be "adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study".

[1] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, Belmont, 1979.

[2] World Medical Association (WMA), *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, Helsinki, 1964 (ed. 2013).

ISSN 2284-4503

It is noted that the potential participant must be informed of their right to refuse to participate in the study or to withdraw their consent at any time without any reprisal. Special attention should be given to the needs of each participant and suitable methods to deliver trial information.
The Declaration goes on to state that only after confirming that an individual has understood the information provided, should voluntary consent be obtained - preferentially in writing, although non-written consent is acceptable as long as it is formally documented and witnessed.
The Guideline for Good Clinical Practice[3] mentions:

- "4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.
- 4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable".

These rules highlight the oral information exchanged between the research team and the participant, and state that both oral and written information must be understandable.
The informed consent document will aim to describe all the information a potential participant needs to autonomously decide whether or not to participate in the study in simple language, using non-technical terms. However, the informed consent process has become highly regulated, and whilst vital to comply with ethical and legal standards, this has resulted in very long and complex consent documents, seen as a 'contract' between the sponsor, the researcher and the participant rather than an informative document.
Given the complexity of contracts in general, usually written by lawyers, potential participants frequently state that the oral information provided by the research team is more important than the written documents. This conflicts with ethical standards because:

1. The written information provided to the participant is not understandable and uses many medical-legal terms.
2. The oral information provided to the participant is not traceable, and is beyond scrutiny from Ethics Committees or health inspections. This is the only process within clinical trials, where no efforts are made in the traceability of information.

2. The need for changes to the informed consent process

According to international ethical guidelines by the Council for International Organizations of Medical Sciences (CIOMS) for health-related research involving humans[4], the concept of informed consent is understood as a process rather than a document. It is considered as "a two-way communicative pro-

[3] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2).* 2016.
[4] Council for International Organizations of Medical Sciences (CIOMS), I*nternational Ethical Guidelines for Health-related Research Involving Humans,* Geneva, 2016.

ISSN 2284-4503

cess that begins when initial contact is made with a potential participant and ends when consent is provided and documented". These guidelines also state that "participants should be offered the opportunity to ask questions and receive answers before or during the research", extending the communicative process throughout the course of the study.

The i-CONSENT project has been developed from the perspective of this new paradigm, in which the research participant is central to the informed consent process. The objective of this project is to develop guidelines to help researchers utilise bidirectional and continuous communication during the process of informed consent, without losing sight of vulnerable populations, multiculturalism and gender perspectives. This process begins at the point of the first contact with the potential participant and continues through to the delivery of study information, discussions with the research team, the decision making process, the intervention and concludes with the follow-up after the completion of the study. Continuous communication allows for the experiences of the participant to be feedback to the research team, which can lead to improvements to the consent process in both current and future studies. The development of guidelines requires collaboration from the different parties involved in clinical trials such as sponsors, researchers and participants.

The theoretical framework of informed consent was extensively studied. Ethical recommendations[5], as well as legal norms at both a national (Spanish, German, French, British, Austrian and Italian[6]) and European[7] level were reviewed. Scientific publications on the process of informed consent in adults, in minors and from the perspective of gender and different cultures were also considered.

From the review of scientific publications, we have observed the importance of the health literacy of the population as a key element when participating in a clinical trial[8], since it allows individuals to ob-

[5] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans. 4ª ed.* Geneva, 2016; World Medical Association (WMA), *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, Helsinki, 1964 (ed. 2013); Department of Health and Human Services, *Code of Federal Regulations. Protection of Human Subjects. 45 CFR 46*, 2009.

[6] *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los Ensayos Clínicos con Medicamentos, los Comités de Ética de la Investigación con Medicamentos y el Registro Español de Estudios Clínicos*, in *Boletín Oficial del Estado Nº 307*, 2015; *Ley 14/2007, de 3 de julio, de Investigación Biomédica*, in *Boletín Oficial del Estado, nº 159*, 2007; *The Medicine for Human Use (Clinical Trials) Regulation n. 1031/2004; Decreto Legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clínico; Gesetz ber den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG), 2005; Code de la Santé Publique; Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).*

[7] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use.

[8] D.G. Scherer, R.D. Annett, J.L. Brody, *Ethical issues in adolescent and parent informed consent for pediatric asthma research participation,* in *J Asthma,* 44(7), 2007, pp. 489-496; L.R. Nelson, N.W. Stupiansky, M.A. Ott, *The Influence of Age, Health Literacy, and Affluence on Adolescents' Capacity to Consent to Research*, in *J Empir Res Hum Res Ethics*. 11(2), 2016, pp. 115-121; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research*, in *BMC Medical Ethics*, 16(1), 2015, p. 76; H. Kim, B. Xie, *Health literacy and internet- and mobile app-based health services: A systematic review of the literature,* in *Proceedings of the Association for Information Science and Technology*. 52(1), 2015, pp. 1-4; G. Quaglio, K. Sorensen, P. Rubig, L. Bertinato, H. Brand, T. Karapiperis, et Al., *Accelerating the health literacy agenda in Europe*, in *Health Promotion International*, 32(6),2017, pp. 1074-1080 (Epub

ISSN 2284-4503

tain, process and understand the necessary information to make an informed and autonomous health decision. In order to facilitate this process, it is necessary to provide clear and concise content which is adapted to the age and capacity of the person to whom it is addressed[9]. Efforts should be made to ensure that the potential participant has understood this information[10]. The format used to present information influences the comprehension of the information and, therefore, the format that best suits the characteristics of the participants must be used. It is recommended that technical language is avoided; that written information is simple, using short and direct phrases and where possible using pictures, photographs and / or easy to understand graphics that support the information[11].

Equally important in the informed consent process is the relationship between the researcher and the participants. Researchers should seek to establish a positive relationship with participants, which is patient-centred. They should seek to establish a climate of trust and avoid the use of non-verbal communication that suggests hierarchy. This approach promotes a socio-emotional and personal exchange that facilitates communication between the patient and the research team[12]. Researchers

2016/04/22); K. Sorensen, J.M. Pelikan, F. Rothlin, K. Ganahl, Z. Slonska, G. Doyle, et al., *Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU)*, in *European Journal of Public Health*, 25(6), 2015, pp. 1053-1058 (Epub 2015/04/07).

[9] *Reglamento (UE) Nº 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre los Ensayos Clínicos de medicamentos de uso humano*, 2014.; A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing study information to children and adolescents: is what they want, what their Parents think they want?*, in *Academic Pediatrics*.18(4), 2018, pp. 370-375; E.S. Dove, D. Avard, L. Black, B.M. Knoppers, *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, in *BMC Medical Ethics*, 14:5, 2013. Epub 2013/02/01; J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials*, in *Cancer*, 119(23), 2013, pp. 4154-4161.

[10] L.R. Nelson, N.W. Stupiansky, M.A. Ott, *The Influence of Age, Health Literacy, and Affluence on Adolescents' Capacity to Consent to Research*, pp. 115-121; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research;* T.A. O'Lonergan, J.E. Forster-Harwood, *Novel approach to parental permission and child assent for research: improving comprehension*,in *Pediatrics*, 127(5), 2011, pp. 917-924. Epub 2011/04/27; S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad, et al., *Comprehension of a simplified assent form in a vaccine trial for adolescents*, in *Journal of Medical Ethics*, 39(6), 2013, pp. 410-412. Epub 2013/01/26; Y. Unguru, A.M. Sill, N. Kamani N., *The experiences of children enrolled in pediatric oncology research: implications for assent*, in *Pediatrics*, 125(4), 2010, pp. 876-83; R.D. Poston. *Assent Described: Exploring Perspectives From the Inside*, in *Journal of Pediatric Nursing*. 31(6), 2016, pp. 353-365. Epub 2016/07/13.

[11] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials*, pp. 4154-4161; D.A. Murphy, D. Hoffman, G.R. Seage 3rd, M. Belzer, J. Xu, S.J. Durako, et al., *Improving comprehension for HIV vaccine trial information among adolescents at risk of HIV*, in *AIDS Care*, 19(1), 2007, pp. 42-51; A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, in *Paediatric Nursing*, 20(6), 2008, pp. 14-18; P. Grootens-Wiegers, M.C. de Vries, M.M. van Beusekom, L. van Dijck, J.M. van den Broek, *Comic strips help children understand medical research: targeting the informed consent procedure to children's needs*, in *Patient Education and Counseling*, 98(4), 2015, pp. 518-524 (Epub 2015/01/24).

[12] Y. Unguru, A.M. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent*, pp. 876-83; R.D. Poston, *Assent Described: Exploring Perspectives From the Inside*, e353-

must also consider how to adapt communication and / or information in the case of minors too young to legally consent, but from whom assent is important; and pregnant women who may require special protection from risks to the foetus, using cultural mediators to aid communication with people of different cultures and / or religions[13].

3. Participants' opinion of the informed consent

To aid the development of the guidelines, a workshop was held with nine representatives of eight patient groups from five different countries (UK, Italy, Spain, Ireland and the Netherlands) and members of the i-CONSENT project team.

The workshop was focused on four themes: comprehension, patient's expectations of participation, assent in the case of minors and gender perspectives. Nominal Group Technique (NGT) was used to collect the perspectives of patient group representatives and to identify and prioritise the issues relating to the informed consent process. NGT is a highly structured, face to face technique which allows consensus to be reached in a group setting.

For each theme, the hypothetical situation of an individual participating in a clinical vaccine trial was used, and meeting attendees considered the issues relating to each theme in turn. Following NGT, attendees were asked to individually and silently generate ideas on paper, before sharing their ideas with the group. At this stage, each of the ideas were clarified and then the attendees individually ranked the issues from each of the themes in priority order.

The findings from the "comprehension" theme showed that for patients, there needs to be a clear case for their participation in a trial, involving a compelling patient story, and an appreciation of the emotional responses of patients/parents.

The clarity of the content and the format used to present information were also considered to be very important. The complexity of a sample informed consent document (read by participants before the workshop) was much criticized for the difficulty in understanding it, and this was felt to be crucial in a participant's decision on whether to participate or not.

Regarding the patient's expectations of participation in a vaccine trial, the attendees considered that the patient's understanding of the study and the informed consent process, as well as the relationship established with the research team were key factors in encouraging participation in a vaccine trial. They valued the direct benefits of participation (e.g. protection against disease from a vaccine, receiving a vaccine free of charge) and the awareness of protection against a serious illness as being important motivating factors for participation.

---

e365; V.A. Miller, J.N. Baker, A.C. Leek, D. Drotar, E. Kodish, *Patient involvement in informed consent for pediatric phase I cancer research*, in *Journal of Pediatric Hematology/Oncology,* 36(8), 2014, pp. 635-640.

[13] Council for International Organizations of Medical Sciences (CIOMS), I*nternational Ethical Guidelines for Health-related Research Involving Humans. 4ª ed.* Geneva, 2016; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research*; P.E. Ekmekci, B. Arda, *Interculturalism and informed Consent: Respecting Cultural Differences without Breaching Human Rights*, in *Cultura*, 14(2), 2017, pp. 159-172.

ISSN 2284-4503

On the other hand, when considering factors that might discourage patients from participating in a vaccine trial, attendees considered the negative perceptions of vaccines, caused mainly by rumours, negative news stories and anti-vaccine campaigners as being the most off-putting factors. Following this, infrequent but significant risks, were also considered to be important dissuading factors, which underlined the importance of accurately communicating risk to benefit ratios.

On the theme of "assent in minors", the attendees discussed how the consent / assent process involves the minor, his/her parents and the research team. Attendees felt there was a greater need to verify the child's understanding as a possible participant in a vaccine trial, perhaps due to a heightened responsibility to protect children due to their vulnerability. Family dynamics were also considered important because the way that decisions are made within families regarding the child's participation can be influenced by social and cultural contexts. They considered that the best scenario is one in which a decision is made jointly between the child and their parents. The third issue considered in order of priority was clear and honest communication with the researcher, which should be adapted to the child's age and capacity.

The last topic was the consideration of "gender" in the informed consent process. The participants were less concerned with this issue, although some attendees favoured communication between participant-investigator of the same sex as they felt this could be more effective (for example adolescent girls may prefer to learn about a trial vaccine against a sexually transmitted disease from a female investigator). In general, they preferred not to attribute characteristics to the behaviour of men and women. The role of both individuals within a relationship were also considered, particularly in the case of a pregnant woman's decision of whether or not to participate in the clinical trial. While one participant felt that the views of both parents should be considered when a pregnant woman is involved, others felt strongly that the pregnant woman's autonomy must be prioritised, and formally consulting partners could jeopardise the rights of the woman to make decisions about her own body. Such differences in the opinions perhaps existed due to social and cultural differences among the meeting attendees.

4. Conclusion

It is recommended to involve the target population in the design of the informed consent process. The informed consent process must connect with participants from the first contact, ensuring that individuals feel their participation is relevant and significant for the research and clearly stating whether through participation, they will obtain protection against a disease.

From this first contact, a truly effective communication relationship must arise in which clear and simple information is presented, avoiding long and complicated documents with technical language and providing a balanced view of the risks and potential benefits, including comparisons with situations that are more familiar to patients. The relationship of communication with the researcher and the trust that it generates between the researcher and patient are key to decision-making and the subsequent development of the research until the end of the study. It is important to increase health literacy throughout the process, to reduce the impact of rumours and erroneous information. After

completing the study, the participant must be informed of the main results, demonstrating the importance of their participation.

In the case of minors, the ideal scenario is the group relationship between the child, his/her parents or legal guardians and the research team. Unstructured family dynamics and family hierarchy could be a barrier. It is recommended that communication is adapted to the child's age and capacity, evaluating his/her understanding and taking into account that digital media could be useful.

Gender stereotypes should be avoided and communication should be adapted to the needs of the participant.

All these aspects have been collected and taken into account in the framework of i-CONSENT project "*Improving the guidelines of Informed Consent, including vulnerable populations, under a gender perspective*" (H2020- Grant Agreement number 741856; https://i-consentproject.eu/).

ISSN 2284-4503

ANEXO 2: Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements.

Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements

Jaime Fons-Martínez, Fernando Calvo Rigual, Javier Díez-Domingo, Leonardo Nepi, Loredana Persampieri, Cristina Ferrer-Albero[*]

ABSTRACT: From an ethical and legal point of view, the assent of the minor to participate in a medical study is a subject of great importance. There is still a debate about the requirements to consider this assent valid and binding. This review analyses and compares the contents of the assent from the points of view of the legislation and the scientific literature.

KEYWORDS: Assent; bioethics; clinical research; hard law; informed consent

SUMMARY: 1. Introduction – 2. Objective – 3. Material and method – 4. Results and discussion – 5. Conclusion.

1. Introduction

Informed consent is one of the fundamental pillars of clinical research ethics, guaranteeing the autonomy of the potential participant in his/her decision to participate or not in an investigation. It consists in a communicative process and a document. The purpose of the informed consent is to protect the autonomy and voluntariness of the potential participant by informing him/her about all the relevant aspects of the study, before enrolment. The consent to participate can be revoked by the participant at any time.

International, European and National legal frameworks recognize both the importance of including children in clinical trials and the need to provide effective and specific protection for this vulnerable group. The best interest of the child is fundamental: this key principle, recognized by the United Na-

* *Jaime Fons-Martínez: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: fons_jai@gva.es; Fernando Calvo Rigual: Servicio de Pediatría Hospital Lluís Alcanyís. Valencia. E-mail: calvo_fer@gva.es; Javier Díez-Domingo: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: jdiezdomingo@gmail.com; Leonardo Nepi: Libera Università Maria Ss. Assunta (LUMSA). Roma. E-mail: nepil@hotmail.it; Loredana Persampieri: Libera Università Maria Ss. Assunta (LUMSA). Roma. E-mail: l.persampieri@lumsa.it; Cristina Ferrer-Albero: Facultad de Enfermería. Universidad Católica Valencia San Vicente Mártir (UCV). Valencia. E-mail: cristina.ferrer@ucv.es. The article was subject to a double-blind peer review process.*

This paper is an extension of the oral communication entitled "Contenidos del asentimiento del menor en investigación médica: diferencias entre la literatura científica y el requisito legal" presented on the V ANCEI Congress, held in Valencia on May 17th and 18th, 2018, and published in their book of papers in Spanish.

This essay is developed within the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), funded by the European Union framework program H2020 (Grant Agreement n. 741856).

tions Convention on the Rights of the Child of November 20, 1989, has inspired the regulation of clinical trials involving minors at European and national levels.
The informed consent in studies with minors is made up of two parts: the minor's parents or legal guardians[1] have to accept the minor's participation in the study, through the parental informed consent; the child should agree to participate in the study, through the assent (if deemed able to do it). Therefore, the decision-making and legal responsibility of the minor's participation in the study is on the parents, but the minor's opinion is taken into account and, depending on the national legislation, he/she could be required to accept/refuse participation.
The hard law and the scientific literature deal with many aspects of assent, such as its possibility; the conditions to conduct a medical study with minors; the need of the parental consent; aspects about the child's age; the consideration of the minor as mature; his/her capacity to understand the information or the contents that the assent should include and how it should be presented.
This study analyses the contents of the assent with the perspective of the hard law and the scientific literature.

2. Objective

Analyse and compare the contents of the assent from the points of view of the legislation (hard law) and the scientific literature.

3. Material and method

Legal framework

The hard law analysis adopts a systematic approach in the review of measures, taking into account International, European and National laws.
The analysis begins from the Council of Europe's Convention on Human Rights and Biomedicine of 1997 and Additional Protocol concerning Biomedical Research, then continues with the analysis of the European legal framework, both at the EU level and in six countries: Austria, France, Germany, Italy, Spain and United Kingdom.
The search strategy contains documents from 2001. It includes general legal framework of mature minor's role on health care decision-making process; case law on D2001/20/CE or R 1901/2006 or R 536/2014 with regard to the informed consent process/assent of minors; case law with regard to the application of EU legislation in selected countries. Measures of transposition of the Directive were taken and implementing rules of European Regulations where implemented. The aim of the search was to identify and analyse the contents of the Informed consent/Assent by minors.
The databases used are Eurlex for the European Law and transposition measures in National regulation[2]; IURE for the European case Law; n-Lex for the national regulation on assent; Iurifast and Dec

[1] To facilitate the reading of the text, we will refer to the parents only from this moment, but it also includes the legal guardians of the minor.
[2] Search as described in http://eur-lex.europa.eu/collection/nlaw/mne.html?locale=en (CELEX number search).

ISSN 2284-4503

Nat for the member State case law which deal with the application of EU law; and the Common Portal of Case Law[3] for the national case law.
The search, screen and decision of including or not a result of finding has been done by pairs of reviewers by members of the LUMSA research unit involved in the i-CONSENT project.

Scientific Literature

Systematic search with PubMed[4] of experimental, observational and theoretical articles (case reports were excluded); published in English or Spanish; during the last 10 years; that include aspects about the information that is given or should be provided to the minor during the assent process in research.
Review of articles resulting from the search was done by pairs (by title and abstract), discrepancies were resolved by a third person. A critical reading and summary of the selected articles was made, with assignation of quality of the article, using the Osteba's Critical Appraisal Tools[5]. The review of the scientific literature was done by members of the FISABIO and UCV research units involved in the i-CONSENT project. The search in Pubmed was done on the 10th of July of 2017.

4. Results and discussion

Legal framework:

International and European legislation

The Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention)[6] in its article 6, highlights the importance of the assent of the minor to any intervention in the health field, indicating that even the authorization should be given by the representative of the minor or an authority or a person or body provided for by law, the opinion of the minor will be taken into account, in proportion to his age and maturity. The EU Charter of Fundamental Rights[7] also expresses the importance of letting minors express themselves freely and taking their opinion into account in accordance with his/her age and maturity.
Regulation (EU) 536/2014[8] indicates the minimum contents of informed consent for clinical trials (article 29, section 2), and the requirements to obtain consent. According to it, informed consent must include: the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

[3] http://network-presidents.eu/rpcsjue/ using Eurovoc Thesaurus (Edition 4.3)
[4]The search strategy used in Pubmed was: ((("Informed consent"[Mesh] OR "assent"[All Fields]) AND "Ethics"[Mesh] AND ("Research"[Mesh] OR "clinical research"[All Fields])) OR (("Informed Consent By Minors"[TW] OR "Consent Forms"[TW] OR "assent"[All Fields]) AND ("Ethical Theory"[TW] OR "Principle-Based Ethics"[TW] OR "Ethics,Research"[TW] OR "Research"[TW] OR "Clinical research"[All Fields]))) AND (English[lang] OR Spanish[lang]) AND ("infant"[TW] OR "child"[TW] OR "adolescent"[TW] OR "minors"[TW]) AND ("2007/07/14"[PDat]: "2017/07/10"[PDat]).
[5] http://www.lecturacritica.com (last visited 9 April 2019).
[6] ETS No.164, *Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, 1997.
[7] *Charter of Fundamental Rights of European Union*, 2000 (2000/C 364/01).
[8] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

the subject's rights and guarantees regarding their protection, in particular his/her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; the possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued. The information must be comprehensive, concise, clear, relevant, and understandable to any person, provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. The article also indicates that the information should be provided in an interview with a member of the investigation team. During the interview, special attention must be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. The article 2 of Regulation defines the minor as a "subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent".

Article 32 of that Regulation specifies that the legal guardian of the minor is the one who should authorise the participation of the minor, but also indicates that the minor must receive the information described in Article 29, adapted to his/her age and mental maturity, by researchers or members of the research team with training or experience in dealing with minors. Specific contents are not specified for assent in minors, considered the same as for informed consent. This article also indicates that the minor's involvement in the informed consent procedure shall be adapted to his/her age and mental maturity.

Article 93 of Regulation (EU) 536/2014[9], establishes the right to confidentiality in clinical trials. Regulation (EU) 2016/679[10], in its 8th article stipulates that the minor should be at least 16 years to give the consent to the processing of his or her personal data (national laws may provide a lower age, but not below 13 years old). If he/she is younger than the stipulated age, the authorization will be granted by the minor's legal guardians.

The informed consent is also necessary when biological samples or health data are collected and stored. Biobanking is an important issue to consider in relation to clinical trials. Privacy and data protection in biobanking is essential for securing acceptance of biobank research across Europe. The Article 22 of Council of Europe Convention on Human Rights and Biomedicine of 1997 establishes that "When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures". The European Union's existing regulatory framework in biomedical research, does not have a specific regulation for biobanks. Biobanks are governed under the general regulatory framework for biomedical research. Likewise, the Directive

[9] REGUL ATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, cit.

[10] REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

ISSN 2284-4503

2004/23/EC[11] on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells, does not cover research using human tissue (Recital 11 and Article 1).

National legislation

The analysis of the national legislation shows that not all States considered have already implemented Regulation (EU) 536/20142 and that the age at which the minor is considered mature enough to understand the information and to consent to participate in a clinical trial varies, being a regulated aspect only at the national level (see table 1).

Table 1. Aspects about the age criteria; assent and dissent by country

	AGE CRITERIA	MINORS YOUNGER	MINORS OLDER	ASSENT	DISSENT	NATIONAL LEGISLATION
UNITED KINGDOM	16	Consent must be provided by parents or legal representative	They are considered as competent adults for decisions on clinical trial participation	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	Medicine for Human Use Regulation of 2004[12]
ITALY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	D.lgs. 211/2003[13]
SPAIN	12	Consent must be provided by parents or	Children must give their consent in addition to the	Required for minor over 12 years old	The researcher must respect the minor's dissent	Royal Decree 1090/2015[14]

[11] DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[12] The Medicine for Human Use (Clinical Trials) Regulation n. 1031/2004.

[13] Decreto Legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.

[14] Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de tica de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

		legal representative	consent provided by parents or legal representative			
GERMANY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Required if the minor can understand the nature and implication of clinical trial (case by case approach)	The researcher must respect the minor's dissent if the minor can comprehend the nature and the implications of clinical trial (case by case approach)	Medicinal Product Act 2005[15]
FRANCE	18 or 16 in the case of emancipated minor, not living with parents and eventually having his/her own family	Consent must be provided by parents or legal representative	Emancipated minor is considered as a competent adult in decisions on clinical trial participation.	Not expressly required	The dissent of the child considered sufficiently mature must be taken into account	Public Health Code of 1953 (amended in 2004,2009 and 2016)[16]
AUSTRIA	18	Consent must be provided by parents or legal representative	The consent of the child must be considered in addition to the consent provided by parents or legal representative if he or she is 14 years old and sufficiently mature	Required if the minor is 14 years old and sufficient mature	The dissent of the child considered sufficiently mature must be taken into account	Austrian Medicinal Product Act 185/1983 (emended in 2004)[17]

Source: Compilation by the authors based on the above-mentioned legislation.

[15] Gesetz ber den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG) 2005.
[16] Code de la Santé Publique.
[17] Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).

Regarding the information provided to the minor or his/her legal representative, there is a broad uniformity (table 2), but neither the European legal framework nor the national standards considered take into account the literacy of the minor or his/her family.

Table 2. Information provided to the minor before the beginning of the clinical trial by country

Country	Information provided to the minor
UNITED KINGDOM	According to Medicine for Human Use Clinical Trials Regulations of 2004, the child must receive information according to their capacity of understanding from staff with experience with minors regarding the trial, its risks and its benefits. Paragraph 3 (1) of Part 1 of Schedule 1 establishes in a general way that the person involved in the research must have met with the researcher and been informed of the objectives, risk and inconveniences of the trial and the conditions under which it is to be conducted. The participant must also be aware that they will be involved in the research before starting the treatment. Further information on the content of the information is provided by the BMA guidelines, which are taken into account by the judge in any consequent judgment.
ITALY	Article 4 of Legislative Decree 211/2003 establishes that children must be informed by staff experienced in dealing with minors about the clinical trial, risks and benefits, in an appropriate manner to their capacity of understanding.
SPAIN	According to article 4 of Royal Decree 1090/2015, in the case of patients with special vulnerabilities, including minors, the person participating at the trial shall be informed about the access to the normal clinical practice for his/her pathology. Article 5 indicates that all clinical trial with minors must comply, in addition to the conditions established in Articles 3 and 4 of the Royal Decree, all those listed in Article 32 of Regulation (EU) No. 536/2014 of the European Parliament and the Council.
GERMANY	Chapter 6, Section 40 (4) of the Medicinal Product Act of 2005 indicates that "before the start of the clinical trial, the minor shall be informed, by an investigator who is experienced in dealing with minors who is a doctor or, in the case of a dental trial, a dentist or an adequately experienced member of the investigating team who is a doctor or, in the case of a dental trial, a dentist, about the trial, the risks and benefits, in so far as this is possible, taking into account the minor's age and mental maturity".
FRANCE	Article L- 1122-2 of the Public Health Code of 1953 indicates that non-emancipated minors that will participate in a research, should get infor-

	mation provided in Article L. 1122-1 adapted to their ability to understand. The article L. 1122-1 indicates that the information has to include: the objective, methodology and duration of research; the expected benefits and foreseeable risks, even if the trial ends earlier than expected; possible medical alternatives; the medical care provided at the end of the trial if such assistance is required; the opinion of the committee referred to in Article L- 1123-1 and the authorization of the competent authority referred to in Article L-1123-12; if necessary, prohibition of simultaneously participating in another search; information about how personal data will be handled; information about the right to receive health data held by the investigator; information about the right to refuse to participate in research or to withdraw consent without incurring any harm.
AUSTRIA	According to §42 of Austrian Medicinal Product Act 185/1983, prior to commencing the clinical trial, the minor must receive and understand appropriate information about the nature, significance, scope and risks of the clinical trial. The minor always has to be informed by an investigator who is experienced in dealing with minors, who must take into account the stage of maturity of the child.

Source: Compilation by the authors based on the above-mentioned legislation.

About confidentiality and privacy, domestic laws do not provide specific norms on the condition of minors who exercise these rights through their legal representatives. Following the analysis of applicable European legislation, it is clear that even in the field of scientific research, the specific consent of the person is necessary for the use of their personal data. In the case of clinical trials involving minors, the ability to provide informed consent must be examined also for consent to the handling of data.

It has been observed that, in spite of the fact that, in many aspects, there is uniformity between the different national legislations and with respect to European legislation, in others, there are still discrepancies. Some of these differences are in relevant issues such as the child's participation in the decision-making process.

What does the scientific literature tell us?

The scientific literature presents the assent as a process that respects and promotes autonomy in the child's development, to express his/her opinion and decide on the health or illness processes that affect him/her. The empowerment and the development of their moral capacity for the autonomous exercise of future decisions are pursued[18,19].

[18] B.J. Pinto Bustamante, R. Gulfo Díaz, *Asentimiento y consentimiento informado en pediatría: aspectos bioéticos y jurídicos en el contexto colombiano*, in *Revista Colombiana de Bioética Universidad El Bosque*, 8(1), 2013, p. 154.

[19] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* in *Adolescent medicine: state of the art reviews,* 22(2), 2011, p. 198.

ISSN 2284-4503

Although much has been written about assent, there is still no agreement in several aspects about this topic, such as the quantity and quality of the information that must be provided to the child or the information that they really want and need to know, among others.
In the literature review carried out, 306 results were obtained from the search strategy, but only 10 articles (1 experimental, 6 observational and 3 theoretical) analysed aspects about the information that is provided or should be provided to the minor during the process of informed consent or assent. Of these, 3 were considered to have high quality by the reviewers, 2 medium quality, 4 low quality and 1 was not classifiable due to the lack of data after critical reading, as shown in table 3.

Table 3: Studies on the information of the assent, according to the quality of the evidence

First Author, Year	Quality of evidence[20]	Type of study	Nº subjects
Unguru, 2010[21]	High	Observational study	37 interviews with children (7 – 19 years)
Tait, 2018[22]	High	Experimental study	55 minors/55 parents (minors: 8-12 years; 13-17 years)
Lee, 2013[23]	High	Observational study	123 minors (12 - 17 years)
Dove, 2013[24]	Medium	Observational study	43 paediatric consent forms
Tait, 2017[25]	Medium	Observational study	20 expert stakeholders
Roth-Cline, 2013[26]	Low	Theoretical study	Not applicable
Twycross, 2008[27]	Low	Theoretical study	Not applicable

[20] Considered by the reviewers using Osteba's Critical Appraisal Tools.
[21] Y. Unguru, A.M. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent,* in *Pediatrics*. 125(4), 2010, pp. 876-883.
[22] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?,* in *Academic pediatrics*, 18(4), 2017, pp. 370-375.
[23] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad et al., *Comprehension of a simplified assent form in a vaccine trial for adolescents*, in *J Med Ethics*, 39(6), 2013, pp. 410-412.
[24] E.S. Dove, D. Avard, L. Black, B.M. Knoppers, *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, in *BMC Medical Ethics*, 14(5), 2013, pp. 1-10.
[25] A.R. Tait, M.E. Geisser, *Development of a consensus operational definition of child assent for research*, in *BMC Medical Ethics,* 18(41), 2017, pp. 1-8.
[26] M. Roth-Cline, R.M. Nelson, *Parental permission and child assent in research on children,* in *The Yale journal of biology and medicine,* 86(3), 2013, pp. 291-301.
[27] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, in *Paediatric nursing*, 20(6), 2008, pp. 14-18.

Baker, 2013[28]	Low	Observational study	20 minors/ 57 parents
John, 2008[29]	Low	Observational study	73 children (6-8 years old)
Giesbertz, 2016[30]	Not classifiable	Theoretical study	Not applicable

Source: self-made

Tait and Geisser[31] did a Delphi study with a panel of expert stakeholders to provide consensus about the definition of child assent for research study. They highlight the importance of providing information appropriate to the child's age, taking into account their cognitive and emotional aspects, such as it can be read in the final definition of assent proposed in the study:

"Children who lack the legal authority to provide informed consent per state laws should provide their assent to participate in a research study unless they either lack the cognitive ability, their clinical condition precludes their ability to communicate a choice, or the research holds out the prospect of direct benefit that is only available in the context of the research. Assent is an interactive process between a researcher and child participant involving disclosure of cognitively and emotionally appropriate information regarding, at minimum, why the child is being asked to participate, a description of the procedures and how the child might experience them, and an understanding that participation in the study is voluntary. Children should understand that they can decline participation or withdraw from the study at any time. Assent requires that the child explicitly affirms his or her agreement to participate in a manner that reflects their age-appropriate understanding and that is free of undue influence or coercion. In the absence of an explicit agreement, mere failure of the child to object cannot be construed as assent"[32].

Analysing the information that the assent should include, they consider essential to inform about the reasons why he/she has been chosen to participate; the procedures and how he/she will experience them; the indirect benefits if there is no expectation of personal benefit; and about the voluntariness and the right to revoke at any time. Understanding this basic information is paramount and the child should be aware of how it will affect his/her personal situation. The freedom of the child to decide about his/her participation in the study without any undue influence or coercion was also pointed out. It is interesting to highlight that during the Delphi process the experts suggested to change "must provide assent" with "should provide assent", making it a recommendation more than an obligation.

[28] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et Al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* in *Cancer*, 119(23), 2013, pp. 4154-4161.

[29] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, in *Archives of disease in childhood*, 93(5), 2008, pp. 379-383.

[30] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord, *Personalized assent for pediatric biobanks*, in *BMC Medical Ethics*, 17(59), 2016, pp. 1-7.

[31] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 1-8.

[32] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 4.

Previously, Roth-Cline and Nelson[33] had already sought evidence regarding the information that the assent must contain. In their review of the literature, they found that there is considerable disagreement about important aspects of the assent, such as: "the age at which investigators should solicit assent from children; how to resolve disputes between children and their parents; who should be involved in the assent process; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need; the necessity and methods for assessing both children's understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model"[34].

They noted that the regulations do not specify the information necessary for the assent, but identify factors to take into account when assessing the minors' capacity, such as the age, maturity and psychological state.

They point out that the minor should understand at least why he/she has been asked to participate and the procedures to be carried out, and must agree to participate, whether parents are provided with more detailed information (such as risks, benefits or alternatives), reinforcing the importance of parental permission during the process. They concluded that the amount of information a child should understand should vary with his/her age and maturity, and argue that the model of assent in adolescents should be different from that of younger children; even so, they cannot affirm with scientific evidence the sections of information that must be included in each assent.

Including the same contents in the informed consent and the assent, as stipulated in the regulation, can also be criticized if we take into account the words of Unguru: when he talks about consent for clinical treatment, he notes that informed consent and assent are not the same and that they are based on different terms, informed consent is based on competence, while assent is based on capacity[35]. This difference may also be valid for clinical research where assent or consent requires a more nuanced and refined decisional capacity than in clinical treatment[36].

But one thing is what the legislation, experts in pediatric bioethics and researchers decide, and another one is the information that children consider relevant for themselves. A study conducted by Tait et al.[37] with 55 parent-child dyads compares the information priorities on research among adolescents (13-17 years) and younger children (8-12) and what the parents consider important to their child. They conclude that for minors and parents (what they believe is important for their children) all the contents are important, but they differ in some aspects. The main interests for the children focus on the procedures of the study, confidentiality and the direct and indirect benefits. There are statistically significant differences in the interests depending on the age of the minor. Adolescents prioritise more the information about voluntarism, direct benefits and procedures, than the younger minors. Comparing the importance given by minors to the information and parent's perceptions of what is relevant for their children statistically significant differences are found in the greater im-

[33] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., pp. 291-301.
[34] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., p. 296.
[35] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 198.
[36] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 200.
[37] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?*, cit., pp. 370-375.

portance that children attach to confidentiality and the lesser importance given to the purpose of the study and the direct benefits.

Parent's perceptions about the child's information priorities also vary depending on the age and gender of the child. They consider that girls will be in general more interested in all the information than boys, except in the case of the information about alternatives that parents consider less important for girls under 13 years than for boys of the same age group. Other statistically significant differences by gender are the priorities of information about the procedures (higher in girls than boys in both age groups) and about the purpose of the study, the direct benefits, the voluntarism and the right to withdraw in any moment (higher in adolescent girls). There are also statistically significant differences in parents' perceptions depending on the child's age, considering that adolescent girls give more importance to information about the purpose of the study and the alternatives than younger girls; and that adolescent boys care more about risks and confidentiality than younger boys. The study also shows that children and adolescents make decisions with parents and investigators, and that they perceive a beneficial effect of shared decision-making.

Unguru, Sill and Kamani[38] also studied the children's preferences about information related to research. They found that most children consider important to know why research is done before being asked to enrol in it, and some consider that it would be useful to be able to talk to other children with experience participating in research to help them understand what participation in a study entails. Another important factor that appears in this study is that some minors enrol or remain in studies because they feel pressured by their parents or physicians. More than one third of the children did not feel free to dissent and half of the children believed that they had little, very little or no role in deciding to enrol or not in the study. By asking minors how they can be more involved, they point out several things that the physician can do, such as talking directly to them and not only to their parents; ask them about their concerns; speak in an understandable language for them or do not treat them as children just because of their age.

As for the involvement of the children in the decision-making, in a study conducted by John et al.[39], in 2008, with young healthy children (6-8 years) who had participated in a study on a vaccine, most parents and several children considered that the parents should be the ones making the decision about the children's participation in the study. It was concluded that the majority of children between 6-8 years do not have the ability to understand the factors surrounding a clinical study, with marked individual differences. They highlighted that these important individual differences in understanding among children of this range of age, makes inappropriate to provide them with all the information about the study, and consider very important the role of the parents directing how capable the child is to understand this information and guiding the meeting of the child with the healthcare professionals. The authors indicate that these results cannot be extrapolated for older children.

[38] Y. Unguru, AM. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent*, cit., pp. 876-883.

[39] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, cit., pp. 379-383.

ISSN 2284-4503

Regarding the amount of information, Baker[40] in a qualitative study using coded interviews carried out in 2013, tried to identify how to improve the quality of the Informed Consent Process received from parents and adolescent and young adult patients (aged 14-21 years) in a Phase I pediatric oncology trial. From the interviews carried out with 20 children between 14 - 21 years old and 57 parents, it was extracted that the most frequent suggestions were related to the information given during the assent process. More information was demanded about the risks, benefits, purpose of the study, scientific grounds that justify their participation and objectives and logistical issues specific to Phase I trials. The respondents expressed their willingness to have a process based on honest communication, without technicalities, adapted to the needs of children and their families. They also suggested that the written information included in the informed consent could be sent in advance, that other formats be used in addition to the written one and that they be provided with a summary sheet with the key aspects, which should be kept in mind during the study development. They also appreciate having more time to make the decision; that the physician explains the study several times, ensures their understanding, has a follow-up meeting to allow the family to discuss their options and guides them in the decision about participating.

This personalization of the agreement tailored to the needs of the child has also been proposed by Giesbertz et al.[41] in a theoretical study in which they tried to answer the question about how the content and the process of assent should be personalized to the child in the specific case of biobanks. Although the lack of data of this publication makes its quality unclassifiable, the article states that for the information to be personalized, it must begin with concrete information (that is easier to understand) and continue providing more information at the child's request, according to his/her desires and capacities. It is recommended not to use only the classic written format, but also different techniques and technical innovations and styles. Information technologies can play an important role to facilitate continuous communication.

In an analysis of the thematic content of paediatric informed consent models by Dove et al.[42], performed with Canadian consent forms, they observed a lot of variability between consent forms and that many of them presented important information gaps. For example, some consent forms did not include aspects such as the child's ability to dissent, the possibility to withdraw, details about the transfer and data sharing or the scope of parental right to access information concerning their child. The majority did not consider cumulative or non-physical risks. Some forms presented a lack of specificity about the role of the minor in the decision-making or the procedures to resolve conflicts in the decision-making between parents and minors.

Looking into the importance of understanding, Lee et al.[43] evaluated in 2013 the comprehension of a modified document in text format with supporting images for a clinical trial of Hepatitis B vaccine.

[40] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* cit., pp. 4154-4161.

[41] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord. *Personalized assent for pediatric biobanks*, cit., pp. 1-7.

[42] E.S. Dove, D. Avard, L. Black, B.M. Knoppers. *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, cit., pp. 1-10.

[43] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad, et al. *Comprehension of a simplified assent form in a vaccine trial for adolescents*, cit., pp. 410-412.

They found that only 56% of the children answered correctly all the questions (six). The issues better understood in the assent were those related to randomization and the possibility of withdrawing from the study; the worst-understood issue was the blinding of the choice of vaccine. They suggested that the inclusion of a quiz in the process of assent could have a positive impact to assess the understanding of the information and ensure the complete comprehension of the study.

Twycross, Gibson and Coad[44] tried to establish a formula so that the information provided to the minors involved in research is appropriate. Through meetings with experts conducted during the Research Society's International Nursing Research Conference, a consensus was reached regarding the information that needs to be provided to the minor and the format that the information should have. The National Research Ethics Services (NRES) consider that the following information needs to be provided[45]:

- "What is meant by research (or a project).
- That they are being invited to take part in research.
- Who else will be taking part (and how many).
- That agreement to take part in the study is voluntary (even if their parent/carer has agreed). They can still say no at any time.
- What the research is about.
- What the researcher will do.
- What they have to do.
- How long it will take.
- Any benefits or anything good that will come from the research; if there are none, say so.
- If there is a reward then you should say.
- That the information they provide is private, unless the child discloses that he or she or someone else is at risk of harm.
- A contact person for further information."

The recommendations about the format are[46]:

- "The information should be kept to a manageable length, in keeping with age and development.
- The sheet should be no more than one double-sided A4 page (excessively detailed information sheets can overwhelm participants).
- The leaflets should be designed so that they can be read to the child but are interactive enough for them to engage in the process.
- The language used needs to be appropriate to the age and developmental stage of the child.
- Pictures can be used to increase engagement but ensure they are appropriate to the child's development, prior learning and setting.

[44] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, cit., pp. 14-18.
[45] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 18.
[46] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 16.

- Do not just increase the size of the typeface of an information leaflet originally designed for older children.
- Information leaflets should be printed on the headed paper of the hospital/ institution where the research is being carried out. Plain paper is not acceptable even for young children.
- Information leaflets need to include the information required for informed consent, as set out by NRES. This might mean being creative in the way you phrase the question or provide the information or else the young child might not fully understand."

Many of these recommendations allude to aspects of legibility, both linguistic (grammatical and lexical) and typographic (graphic characters), which will allow the child to read and understand it more easily.

In the same study, Twycross et al. explored other interesting aspects such as the age at which minors can give a "so-called informed agreement" to participate in a research study or how to verify that the minor has understood the information. Concerning the age, they indicated that if the information is presented in an appropriate way, children from 18 months or 2 years old could already give informed agreement to participate in the study. They recommended to verify the understanding of the minor by asking him/her to repeat back to the researcher what the project is about and what their participation will involve, or include a written or picture-based list of questions to be answered at the end of the information sheet.

5. Conclusion

Even if the importance of minors' participation in clinical research is highlighted in the legal and scientific documents, there is a lack of high quality studies conducted in Europe on this topic that make it difficult to draw conclusions. The topic of the contents of the assent has not been explored at depth, probably because the legal texts establish the contents and they are the same as for the informed consent in adults. The focus has been usually put on the adaptation of the content to the age and maturity of the minor, the understanding of the document, the profile of the person who should give this information and the importance devoted to the minor's opinion.

Analysing the European legal framework, the specific issue of informed consent in the context of clinical trials involving minors allows us to identify some key points: a) the rule takes into account the proxy consent that must be provided by parents or other legal representatives; b) Regulation No. 536/2014 (Article 32, Clinical trials on minors) requires the child to receive the information referred to in Article 29(2) in a manner appropriate to their capacity of understanding, provided by staff with experience with minors; c) the explicit dissent to start or continue research participation at any time expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial must be considered by the investigator.

Comparing the legislation with the scientific literature, it has been seen that there are differences in the information that the assent should include from the point of view of the legislators, researchers, parents, and minors (being also different the priorities for adolescents and younger children). There is also a current debate about the convenience of giving the minor all the information (adapted to his/her age and maturity) or giving only some contents to them (also according to his/her age and

maturity and taking into account that all the information is given to parents in their consent). Even so, there are some contents that are identified most of the times as essential in the assent, such as why they have been asked to participate, the study procedures, the voluntariness of participation or the option to leave the study at any time. There is no agreement on the age at which the child's opinion should be taken into account, nor about the role that parents should play during the information phase and the child's decision-making process.

There are differences about the information that the investigators and the parents consider relevant for the minors and that the minors consider relevant for themselves. This should be taken into account when investigators or parents inform minors, as probably they will give the information that they consider relevant to minors and not what minors consider relevant for themselves. The information that the parents deem important for minors is different according to gender and age, so the impact of gender on the information process should also be taken into account when parents inform minors or help them during the decision-making process.

More studies about the interests and needs of the minors are needed to adapt better the contents and the process of assent to them instead of considering that adults and minor have the same needs of information.

In addition to what is said (content and quantity), it is relevant how it is said (method/format used, information order, legibility), who says it (skills of the person reporting), how many times it says it (continuity and adaptation of the information throughout the study) and what the child wants to know or cares about.

It is also essential to ensure an adequate understanding of the information. Additional actions such as personalising the process, talking directly to minors and soliciting their concerns, asking minors to repeat back the information provided, including a quiz in the process of assent or giving him/her the possibility of talking with other minors with previous experience participating in clinical trials may have a positive impact in the process and contribute to ensuring the comprehension of the information and involving minors in the decision-making.

The role of the minor in the decision-making also needs to be better set. The legal documents give importance to the minor's opinion through the assent (depending on their age and maturity), but the scientific literature suggests their lack of influence in the decision-making. Moreover, the scientific literature shows the lack of efforts or mechanisms to ensure that the opinion/wish of the minor to participate in research is taken into account, neither to facilitate the understanding of the information by the minor and their parents. Legal documents have a key role in the consideration and importance given to both aspects, in setting out standards and requirements.

ISSN 2284-4503

ANEXO 3: Digital tools in the informed consent process: a systematic review.

BMC Medical Ethics

RESEARCH ARTICLE Open Access

Digital tools in the informed consent process: a systematic review

Francesco Gesualdo[1*], Margherita Daverio[2], Laura Palazzani[2], Dimitris Dimitriou[3], Javier Diez-Domingo[4], Jaime Fons-Martinez[4], Sally Jackson[1], Pascal Vignally[1], Caterina Rizzo[1] and Alberto Eugenio Tozzi[1]

Abstract

Background: Providing understandable information to patients is necessary to achieve the aims of the Informed Consent process: respecting and promoting patients' autonomy and protecting patients from harm. In recent decades, new, primarily digital technologies have been used to apply and test innovative formats of Informed Consent. We conducted a systematic review to explore the impact of using digital tools for Informed Consent in both clinical research and in clinical practice. Understanding, satisfaction and participation were compared for digital tools versus the non-digital Informed Consent process.

Methods: We searched for studies on available electronic databases, including Pubmed, EMBASE, and Cochrane. Studies were identified using specific Mesh-terms/keywords. We included studies, published from January 2012 to October 2020, that focused on the use of digital Informed Consent tools for clinical research, or clinical procedures. Digital interventions were defined as interventions that used multimedia or audio–video to provide information to patients. We classified the interventions into 3 different categories: video only, non-interactive multimedia, and interactive multimedia.

Results: Our search yielded 19,579 publications. After title and abstract screening 100 studies were retained for full-text analysis, of which 73 publications were included. Studies examined interactive multimedia (29/73), non-interactive multimedia (13/73), and videos (31/73), and most (34/38) studies were conducted on adults. Innovations in consent were tested for clinical/surgical procedures (26/38) and clinical research (12/38). For research IC, 21 outcomes were explored, with a positive effect on at least one of the studied outcomes being observed in 8/12 studies. For clinical/surgical procedures 49 outcomes were explored, and 21/26 studies reported a positive effect on at least one of the studied outcomes.

Conclusions: Digital technologies for informed consent were not found to negatively affect any of the outcomes, and overall, multimedia tools seem desirable. Multimedia tools indicated a higher impact than videos only. Presence of a researcher may potentially enhance efficacy of different outcomes in research IC processes. Studies were heterogeneous in design, making evaluation of impact challenging. Robust study design including standardization is needed to conclusively assess impact.

Keywords: RCT, Informed consent, Innovation, Multimedia, Video, Digital tools, Systematic review

Background

In 1967, the World Medical Association Declaration of Helsinki [1] set the framework for the practical application of the notion of Informed Consent (IC) in clinical research for the years to come. The declaration built upon the foundations put in place by the Nuremberg

*Correspondence: francesco.gesualdo@opbg.net
[1] Ospedale Pediatrico Bambino Gesù (OPBG), Piazza di Sant'Onofrio, 4, 00165 Rome, Italy
Full list of author information is available at the end of the article

Code, which stated that the primary consideration in research is the subject's voluntary consent [2]. After more than a half a century, these principles are still valid.

In clinical research, the IC process is essential for the potential participant to be informed of the fundamental elements of the research protocol, of the possible benefits but also of the risks and of the level of uncertainty relating to the research project, in order to be able to choose freely and consciously [1]. Ethical [3] and legal [4] requirements are clear in recommending and regulating an adequate IC process as a key element of clinical research. In the disclosure of the information, therapeutic misconception [5] or unrealistic optimism of the participant should be taken into account, as they are factors that can prevent the subject from understanding correctly the risks that a clinical study can imply. This can happen because of an overestimation of envisaged benefits deriving from participating in a clinical trial [6] and/or due to misunderstandings concerning clinical research procedures (e.g. about randomization and/or the role of placebos in clinical trials) [7].

On the clinical practice side, providing understandable information to patients is also necessary, in order to achieve the two important aims of respecting and promoting patients' autonomy and protecting patients from harm [8]. In the health care context, the specific function of the IC is to provide an instrument to guarantee a balanced physician–patient relationship: it is an explicit expression and authorization given by the patient to accept (consent) or refuse (dissent) treatments or clinical/surgical procedures offered by the doctor [9]. An intervention in the health field may only be carried out after the patient has given free and informed consent to it [10]. Both in clinical practice and in clinical research, a clear and complete information process, which includes the disclosure of information and its comprehension [11], is the condition for providing a valid consent [12].

Research participants' and patients' comprehension of IC is therefore crucial. Nevertheless, frequently, comprehension can be too limited for an autonomous decision to be made. A meta-analysis conducted on 135 cohorts of participants in clinical trials showed that IC comprehension varied between 52 and 76% for different components [13] and only one third of study participants in pre-surgery studies published before 2006 showed a correct understanding of risks associated with surgery [14]. According to Tam et al., the proportion of participants understanding IC documents has not increased over the past 30 years [13].

IC comprehension can be affected by a number of factors that should be taken into account in designing an adequate IC process.

First, age, gender, and health literacy may affect the communication process and the comprehension of the IC, and therefore bias the decisions taken by patients [15–18]; differences in cultural background among the researcher/physician and the participant/patient can have an influence on the information process [19], and comprehension of the disclosed information can vary in high and low income countries [20].

Secondly, context-dependent factors (e.g. clinical and affective factors) may come into play, for example depending on the clinical conditions of the participant/patient, as in the case of phase I trials, where patients normally do not have another alternative to treatment [21, 22]. Moreover, trust can support the IC process [23] but it cannot overcome the role of the information provided [24]. If trust outweighs information, it may generate the so-called researcher bias [25].

Thirdly, comprehension of IC can be hampered by elements directly related to the format of the information provided to participants. The format affects the readability of consent documents, which is often insufficient [26], due to complex contents and the length of the text.

In this perspective, digital tools can be adopted in IC processes with different potential impacts: improving comprehension of the disclosed information, addressing IC-related issues (e.g. therapeutic misconception, researcher bias) by improving the information process, and improving an informed participation of vulnerable populations in clinical research (e.g. minors, subjects coming from different cultural and religious backgrounds, persons with disabilities) through tailored communication [27]. To facilitate an informed decision, effective techniques are required to communicate abstract concepts such as experimental study methods, and enable their comprehension, as in many cases patients may decide to participate in a study or express satisfaction towards a consent format without having a comprehensive understanding of its contents [28].

Several studies have aimed to improve the access and comprehension of the IC format, by providing information using a diverse range of digital instruments including videos, audio–video formats, and computer-based techniques [29, 30]. Previous published meta-analyses have shown a limited effect of multimedia in improving understanding during the IC process in clinical research [28, 31]; they also reported that interventions on IC through digital or multimedia tools do not negatively affect patients' satisfaction [28, 31]. Several different outcome measures have been taken into account throughout different studies, but results are often inconsistent, and the generalisability of studies is limited; the review by Nishimura reported the need for the identification of best practices of IC interventions for next systematic

comparisons [31]. At present, no evidence of the impact of specific, digitally-supported IC processes is available.

We conducted a systematic review to assess the impact of digitally-supported IC processes on understanding, satisfaction, anxiety and participation compared with non-digital IC processes, in the context of a H2020 funded project dedicated to improving the IC process in biomedical/clinical research (i-CONSENT, Grant Agreement No. 741856). We took into account studies reporting the information process both in clinical research and in clinical/surgical procedures, in consideration of the key role that a correct and understandable information plays in the consent process in both settings (clinical research and healthcare contexts).

Methods

Our study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [32].

Search strategy

We conducted a systematic literature review following an a-priori defined, unpublished protocol. We searched for studies published between 1st January 2012 and 31st October 2020 on available electronic databases including Pubmed, Embase and Cochrane. The term "Informed Consent" and related terms were combined with keywords or Mesh terms related to technologies considered relevant for innovative, digitally supported IC processes (see Additional file 1 for details). The reference list of published reviews were screened for relevant articles meeting the eligibility criteria.

Eligibility criteria

We included studies published from January 2012 to October 2020, with full text available in English, Italian or French, which compared the effect of digital IC vs. non-digital forms of IC (written on paper and/or face-to-face discussion) for participation in research studies or for clinical procedures. Digital interventions were defined as interventions that used multimedia or audio-visual means to provide information to patients. We selected studies focusing on digital tools both for clinical IC (for surgery, diagnostic procedures, therapeutic interventions) and for research IC. Results will be presented in two different sections for these two types of consent.

In order to review more informative and robust studies providing information on the existing differences between digital and non-digital IC processes, we decided to select only articles based on a randomised controlled trial (RCT) study design. Therefore, we excluded articles that reported the results of cohort studies, systematic reviews or meta-analyses.

Study selection

One researcher (PV) screened the titles and abstracts of the unique references to identify potentially relevant papers. After this primary screening, full texts were reviewed to assess eligibility criteria for inclusion in the review.

Data extraction and definitions

Data were extracted by two researchers (CR and PV), using a standardized extraction form. The two datasets were then evaluated and in case of conflicting results a decision was taken through a discussion between CR, PV and a third researcher (AET).

For each study, we extracted the following information: population and setting; type of IC intervention (video, interactive multimedia, non-interactive multimedia); kind of non-digital IC process used in the comparison group; type of study/procedure for which the consent was requested (clinical study, diagnostic test, therapy/vaccine, surgery); outcome measured (knowledge/comprehension/understanding/recall, satisfaction, acceptability, anxiety, study participation) and effect value for the comparison of the intervention and control groups.

For each article, we also reported if the article addressed the concepts of therapeutic misconception or of researcher/clinician allegiance in the recruitment process.

Quality of included studies was assessed using criteria selected through discussion among the involved researchers: sufficient sample size (according to a priori or post-hoc sample size calculation—studies not reporting a sample size calculation were considered as not meeting the criteria); sufficient description (based on researchers' judgement) of RCT or clinical procedure for which the consent was requested, intervention (digital tools in the consent process) and comparison; objective criteria to measure outcome; consideration of limitations (any limitation that affected both study arms equally, e.g. sample size); and consideration of bias (any element producing a differential effect on the two study arms).

Interventions were classified into 3 different categories: video only, non-interactive multimedia, and interactive multimedia. Video was defined as the provision of audio-visual content only. Multimedia interventions were defined as software that provided consent information in various format combinations (images, audio, videos, graphics, etc.). Multimedia interventions were either navigated directly by the patients or used by the researcher as a support during the explanation of the study/procedure. Interaction was defined as patient interaction with the software, eg. providing responses to questions. The non-digital format of the IC process was defined as

reading a paper text presenting the IC and/or a standardized face-to-face discussion.

Regarding outcomes, the reported participation in the clinical study was either an actual participation, when the patient actually signed the IC for participating in the RCT or clinical procedures, or a hypothetical participation where patients declared their potential participation in a future RCT or clinical care procedures. Participant understanding of the IC document was a key outcome that we looked for. Studies meeting our eligibility criteria either referred to "understanding", "comprehension", "knowledge" or "recall". As only a few of the included studies drew a distinction between these terms, in this review paper, we use the term "understanding" to refer to outcomes that may also have been termed "knowledge" and "comprehension". Information retention and information recall were also categorised as understanding.

We classified an intervention as effective on a specific outcome if the article reported a statistically significant effect (irrespective of the effect magnitude) of the studied intervention with respect to the comparison.

Data synthesis

Some of the retrieved data were categorised (kind of study/procedure for which the consent was requested, type of digital intervention, kind of outcome), and descriptive statistics were used to analyse the kind of interventions and main outcomes considered. We present a narrative synthesis of the main results. The positive effect of digital tools on each outcome was presented as the proportion of studies reporting statistically significant results (irrespective of the effect magnitude) on the total studies focusing on that specific outcome. Neutral effect of the digital intervention compared to non-digital IC process was considered as negative.

Results

Results of the literature search

We identified 19,579 publications through electronic search. A total of 16,743 were electronically screened to select clinical trials; after removing duplicates, 1,731 publications were screened for eligibility through reading title and abstract, 100 articles were retained for full text assessment and 73 were included in the review. Details of the study selection process are reported in Fig. 1. Studies included in the review are reported in Additional file 2 and 3.

The majority of the study populations included in the systematic review were adult individuals; 6.8% (5/73) of the studies investigated consent provided for children, and 2.7% (2/73)investigated assent by adolescents. Of the selected studies, 54.8% (40/73) were set in North America, 23.3% (17/73) in Europe, 9.6% (7/73) in Oceania, 9.6% (7/73) in Asia and 2.7% (2/73) in Africa.

Twenty-eight studies (38.4%) investigated digitally supported IC processes for research (see Additional file 2) and 45 studies (61.6%) investigated digitally supported consent processes for clinical/surgical procedures (see Additional file 3).

Overall, 29 studies used interactive multimedia (39.7%), 13 used non-interactive multimedia (17.8%), and 31 used videos (42.5%). Studied outcomes differed among included articles. Thirty-five (48%) articles explored more than one outcome.

With regards to the quality of the included studies, 46 (63.0%) had a sufficient sample size, justified by a power calculation; 70 (95.9%) reported an adequate description of the research/clinical procedure for which the consent was requested, 73 (100%) reported a sufficient description of the intervention and 71 (97.3%) reported a sufficient description of the comparison; 70 (95.9%) used objective criteria to measure the outcome; the researcher responsible for collecting information about the outcome was blinded to group allocation in 21 (29%) of the studies; 54 (74%) considered limitations and 33 (45.2%) considered bias.

Research studies

A total of 28 studies reported results on the efficacy of digitally supported IC processes for research studies (Table 1). Among those, 16 were mock studies. Fifteen (53.6%) used interactive multimedia, 4 (14.3%) used non-interactive multimedia, and 9 (32.1%) used videos. Each of the included articles explored from 1 to 3 outcomes: 24 explored the effect of the digital intervention on understanding, 8 articles explored the effect on satisfaction and 10 on participation in a research study (which was hypothetical in 5 studies). None of the included studies investigated the effect of digitally-supported research IC on anxiety. Among the 28 included articles, 15 (53.6%) reported a positive effect on at least one of the studied outcomes. TMore than a half of studies investigating interactive multimedia interventions reported a positive effect on at least one of the studied outcomes: 8/15 (53.3%) for interactive multimedia interventions and 3/4 for non-interactive multimedia interventions. The proportion of studies reporting a positive effect was slightly lower for videos (4/9). A positive effect was reported in 12 (50.0%) of the 24 studies investigating understanding and in 5 of the 8 studies investigating satisfaction. On the other hand, participation in research studies was improved in 4/10 studies only and 3 out of these 4 were mock studies.

In 14 studies (50%), the researcher was present during the consent process and 9 (64.3%) had at least one

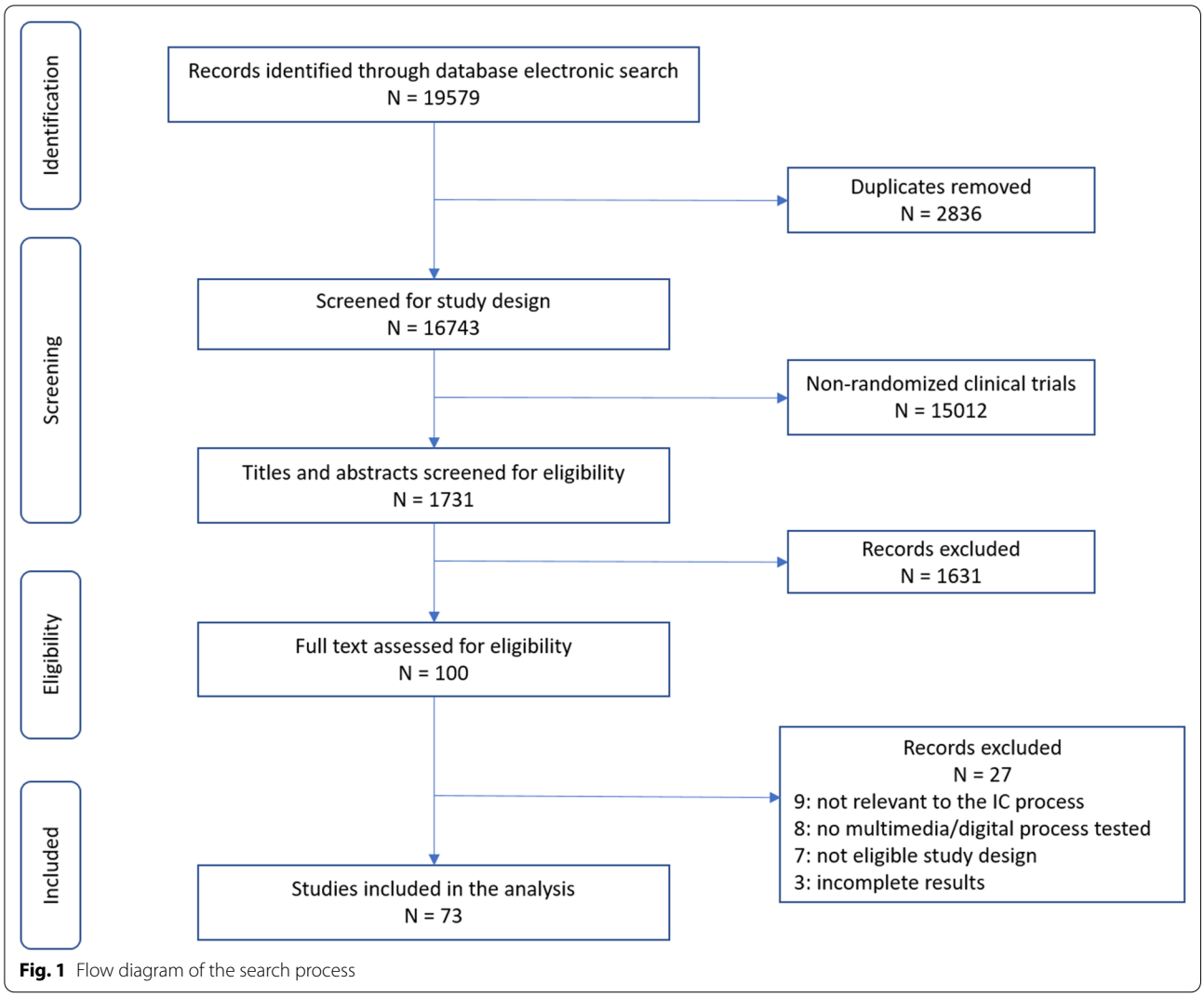


Fig. 1 Flow diagram of the search process

positive outcome. On the other hand, among the 14 studies in which a researcher was not present during the IC process, 6 (42.9%) had at least one positive outcome.

Clinical/surgical procedures

A total of 45 studies reported results on the efficacy of digitally supported IC processes for clinical/surgical procedures (Table 1). Of these, 5 were mock studies. The processes studied in the included articles were aimed at obtaining IC for surgery (86.7%), diagnostic tests (6.7%), and therapy/vaccine (6.7%).

Among these, 14 (31.1%) used interactive multimedia, 9 (20.0%) used non-interactive multimedia, and 22 (48.9%) used videos. Each of the included articles explored from 1 to 4 outcomes: 37 articles explored the effect of the digital intervention on understanding, 25 on satisfaction, 13 on anxiety, and 6 on participation. Of these, 4 were mock studies. The IC under evaluation was developed with the active participation of patients in 2 (4%) of the studies dedicated to clinical IC. Two articles addressed the concept of therapeutic misconception; none addressed the concept of clinician allegiance.

Among the 45 articles considered, 37 (82.2%) reported a positive effect on at least one of the studied outcomes. The efficacy of digitally supported interventions was higher for interactive multimedia interventions (13/14 articles reported a positive effect on at least one of the studied outcomes) and non-interactive multimedia interventions (8/9 articles reported a positive effect on at least one of the studied outcomes); and lower for videos (only 16/22 studies reported a positive effect). The effect was generally positive for understanding and satisfaction (75.7% and 60.0% of the studies reported a positive effect respectively), and lower for anxiety (30.8% of the studies reported a positive effect). Four out of 6 studies investigating participation reported a positive effect of

Table 1 Description of the positive effect of each investigated outcome (articles explored more than one outcome) by type of digital intervention and study

	N of studies	Understanding		Participation in the study/ consent to clinical procedure		Satisfaction		Anxiety		At least one positive outcome	
		Positive/total	Percent positive	Positive/total	Percent positive	Positive/total	Percent positive	Positive/total	Percent positive	Positive/total	Percent positive
Research studies											
Video	9	2/7	28.6	1/4	25.0	1/1	100.0	–	–	4/9	44.4
Other multimedia non interactive	4	2/3	66.7	1/1	100.0	–	–	–	–	3/4	75.0
Multimedia interactive	15	8/14	57.1	2/5	44.0	4/7	57.1	–	–	8/15	53.3
Total	28	12/24	50.0	4/10	40.0	5/8	62.5	–	–	15/28	53.6
Clinical procedures											
Video	22	13/18	72.2	1/2	50.0	8/14	57.1	2/7	28.6	16/22	72.7
Other multimedia non interactive	9	5/7	71.4	1/1	100.0	3/6	50.0	2/3	66.7	8/9	88.9
Multimedia interactive	14	10/12	83.3	2/3	66.7	4/5	80.0	0/3	0.0	13/14	92.9
Total	45	28/37	75.7	4/6	66.7	15/25	60.0	4/13	30.8	37/45	82.2
All studies											
Video	31	15/25	60.0	2/6	33.3	9/15	60.0	2/7	28.6	20/31	64.5
Other multimedia non interactive	13	7/10	70.0	2/2	100.0	3/6	50.0	2/3	66.7	11/13	84.6
Multimedia interactive	29	18/26	69.2	4/8	50.0	8/12	66.7	0/3	0.0	21/29	72.4
Total	73	40/61	65.6	8/16	50.0	20/33	60.6	4/13	30.8	52/73	71.2

the digitally-supported intervention; in two of the positive studies consent to the procedure was hypothetical. Among the 34 studies in which the researcher was present during presentation of IC, 27 (79.4%) had at least one positive outcome, compared with 10/11 (90.9%) in those in which a researcher was not present.

Discussion

The objective of the present review was to compare the effect of digitally-supported vs non-digital IC processes on different outcomes, namely understanding, satisfaction, anxiety, participation (either real or hypothetical). Digital tools for IC published in the medical literature from January 2012 to October 2020 fell into three main categories: videos only, non-interactive multimedia tools, and interactive multimedia tools. Included studies were very heterogeneous in terms of study population, intervention, outcome measures and results. While we were unable to perform a meta-analysis due to heterogeneity in study designs, we found that the digital technologies evaluated in this review did not affect any of the outcomes negatively, and a positive—although limited—impact was observed for multimedia tools than videos only, for which impact appears lower.

We found fewer studies on digitally supported consent for research than for clinical care (surgery, therapy, vaccines, diagnostic procedures). Few articles on consent in research evaluated participation as an outcome and, in half of the cases, participation was only hypothetical. This observation suggests that studies for evaluating the impact of digital tools for the consent process, in particular for research projects, using an experimental design and including participation as an outcome should be promoted, embedding them into planned clinical trials.

Most included studies explored the added value of digital tools for obtaining consent in adult populations. Articles dedicated to consent (and assent) for studies or procedures involving children, adolescents and other minority groups (e.g. pregnant women, elderly individuals, persons with disabilities) were less represented, highlighting the need of focusing future research on these population subgroups [33, 34].

Previous reviews reported inconsistent conclusions about the use of audio-visual aids for IC [28, 31, 35]. Our review suggests that digital tools have a higher impact on IC for clinical procedures than for participation in research studies. Moreover, both in clinical research and in clinical/surgical procedures, multimedia tools seem to have a higher impact on improvement of outcomes of the IC process. One reason for this could be that the information provided in videos does not add much beyond the information already provided in person by clinicians and researchers, while combining different multimedia formats (slides, audio, video, graphics) and engaging the patient through interaction with the digital technology (mainly questions to verify understanding), seemed to improve both satisfaction and understanding (subjective and objective). The value of interaction of the patients with digital tools deserves further research, as preliminary results seem promising [36].

Presence of the researcher/clinician during the digitally-supported IC process varied across the included studies. When considering research consent, our review suggests that the presence of the researcher may enhance the efficacy of digitally supported consent processes. The mechanism for this was not established in this study, but we hypothesise that this could be due to the direct interaction between participants and researchers (e.g. question and answer). This supports the findings of Flory et al. [28], that person-to-person interaction has a high impact on understanding. On the other hand, the adoption of digital tools may facilitate addressing issues related to the IC process (e.g. therapeutic misconception, researcher bias) by guaranteeing self-standing information alongside with the presence of the researcher. Future research should focus on the role of the researcher in digitally-supported IC processes, with the aim of better specifying what is the right balance between the researcher's contribution to participants' comprehension of IC documents and the potential biases associated with human-mediated IC processes.

Conversely, the majority of studies on clinical and surgical procedures found that physical presence of the researcher does not add any benefit; which would lend support to the concept of a self-administered, digital consent in clinical and surgical procedures, which could reduce clinicians' opportunity costs through time saved.

Understanding was the most described outcome, followed by satisfaction, participation and anxiety. Generally, understanding was positively affected by digitally-supported IC processes, both for research and for clinical procedures. Anxiety was not considered in any of the studies that investigated research IC, and results on the impact of digital technologies for clinical IC on anxiety were inconclusive.

Although we classified digital tools into different categories, technologies within the same category may differ in quality and/or performance. Quality could be affected by a range of factors that were usually not reported, including how the information presented was selected, the design of the tool including graphics, and the length of time given to the consent process. Outcomes and setting were also heterogeneous, making comparisons of effect between studies difficult. Different dimensions of communication should be considered when planning future studies on this topic. An attempt to standardize at

least some of the outcomes would be helpful for supporting decisions to use digital tools.

We only found two studies that evaluated the effect of digital tools for research IC in developing country settings [37]. Both compared multimedia ICs (one interactive and one not) with traditional paper-based consent methods, and showed positive effect on understanding with respect to paper-based traditional ICs. In some developing country settings, patients have accepted to participate in trials despite having a limited understanding of a study, with their decision being influenced by concerns about potential consequences of refusing to participate [20]. In such contexts, it is unclear whether an improved understanding through of the digital tools would alter participation.

We also explored the inclusion of patients in the creation of the digital ICs across the included articles. Participatory approaches have previously been used to include patients in the design of IC material and processes, mainly through focus groups, in particular to address issues related to readability and understanding of the IC documents [38]. Among the studies included in our review testing digitally supported IC for research, patients were involved in the development of the IC through focus groups [39, 40], through participation in iterative review processes [41, 42] or through a direct involvement in the production of IC videos [41–43]. The use of innovative methods for a more frequent, deeper involvement of patients in the design of IC for research is advisable. We previously reported on a mixed-method approach for patient involvement, mainly based on design thinking techniques [44]. This may help to empower patients in discussing clinical decisions with clinicians and in avoiding inequities in healthcare, as suggested by other experiences in participatory healthcare [7].

This systematic review gave us some insights about the potential limitations of the adoption of digital technologies for IC. Technology evolves constantly, and the continuous change in available tools makes keeping track of tools challenging. A repository of available innovative, digital tools with a constant update system would be desirable. In addition, the digital divide has been reported to act as a barrier to access for some segments of the population such as the elderly, people from low income and minority populations, or persons with disabilities [45–47]. Additional considerations may be necessary to ensure inclusion of these populations and caution should be posed to avoid marginalization of minorities [48].

This study has a number of limitations. Study heterogeneity made inter-study comparison problematic: while we attempted to grade study quality, it was difficult to conclusively distinguish one study as being of higher quality than another, which also made it challenging to gauge the relative quality of the tools reported. We were able to broadly observe trends, but were unable to perform a meta-analysis of the results. Developing standard methods for studying and comparing digitally supported ICs (in particular for research projects) would facilitate better evaluations of innovative consent tools in the future. Moreover, we did not find a systematic evaluation of costs in any of the studies included in the review. As the investment for developing digital tools reflecting the content of the IC should be balanced with the return in terms of efficacy in improving understanding, this outcome would deserve more attention.

Conclusions

The objective of IC is to meet patients' needs for clear and complete information. In recent years, the use of digital tools for improving participants'/patients' understanding and satisfaction of the IC seems to have had an impact. Digital tools, particularly interactive multimedia tools, may be useful in enabling the development of personalised IC that is tailored to an individual's socio-cultural characteristics. Currently, studies are heterogenous. Developing standardised methods for the assessment of impact of digitally supported IC processes, including recommendations for researchers in this field, would facilitate better evaluation of innovative consent tools in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12910-021-00585-8.

Additional file 1: Search strategy. The document shows the search strings used on PubMed and on EMBASE, and a list of systematic reviews screened for additional results.

Additional file 2: Description 1. Description of the studies included in the systematic review evaluating digitally supported IC processes for clinical research. Table showing characteristics of included studies evaluating digitally supported IC processes for clinical research and list of references.

Additional file 3: Description 2. Description of the studies included in the systematic review evaluating digitally supported IC processes for clinical/surgical procedures. Table showing characteristics of included studies evaluating digitally supported IC processes for clinical and surgical procedures and list of references.

Abbreviations

IC: Informed consent; RCT: Randomised controlled trial; WoS: ISI web of science; PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Acknowledgements

This work was conducted by members of the i-Consent project: https://i-consentproject.eu.

Authors' contributions

FG, AET and SJ conceptualized the study and wrote the paper; MD wrote the introduction and revised the paper; CR and PV screened titles and abstracts

and extracted data; in case of conflicting results, a decision was taken by AET. LP, DD, JDD, JF and CR participated in interpretation of the data, revising the manuscript and providing approval of final manuscript. All authors have read and approved the manuscript.

Funding
This research was funded by the European Union H2020 programme, as part of the work of the i-Consent project (i-CONSENT, Grant Agreement No. 741856). The funding covered the resources for the present systematic review, which was one of the deliverables of the i-CONSENT project.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1] Ospedale Pediatrico Bambino Gesù (OPBG), Piazza di Sant'Onofrio, 4, 00165 Rome, Italy. [2] Libera Università Maria Ss. Assunta (LUMSA), Via della Traspontina, 21, 00193 Rome, Italy. [3] AND Consulting Group SPRL, Place Marcel Broodthaers, 8, 1060 Brussels, Belgium. [4] The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Avda. de Catalunya, 21, 46020 Valencia, Spain.

Received: 4 June 2019 Accepted: 15 February 2021
Published online: 27 February 2021

References

1. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ. 2001;79:373–4.
2. Annas GJ. Beyond Nazi war crimes experiments: the voluntary consent requirement of the Nuremberg code at 70. Am J Public Health. 2018;108:42–6.
3. World Health Organization. Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2017.
4. Parliament E, Union the C of the E. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16. on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. J Eur Union. 2014;2014(57):L58–61.
5. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. IRB. 2004;26:1–8.
6. Palazzani L, Rinella A, Macioce F, Nepi L, Persampieri L, Ferro V, et al. Legal issues concerning informed consent in translational/clinical research and vaccination. 2018. https://i-consentproject.eu/wp-content/uploads/2019/01/D1.5-Legal-issues-concerning-informed-consent-in-translationalclinical-research-and-vaccination.pdf.
7. Blease CR, Bishop FL, Kaptchuk TJ. Informed consent and clinical trials: where is the placebo effect? BMJ. 2017;356:j463.
8. Jefford M, Moore R. Improvement of informed consent and the quality of consent documents. Lancet Oncol. 2008;9:485–93.
9. Palazzani L. Informed consent, experimentation and emerging ethical problems. BioLaw J Riv BioDiritto. 2019;16:11–22.
10. Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research. Jahrb Für Wiss Ethik. 2005;10. https://doi.org/10.1515/9783110182521.391.
11. Beauchamp TL, Childress JF. Principles of biomedical ethics/Tom L. Beauchamp, James F. Childress. 4th ed. New York: Oxford University Press; 1994.
12. International Bioethics Committee. Report of the International Bioethics Committee of UNESCO (IBC) on Social Responsibility and Health. UNESCO; 2010.
13. Tam NT, Huy NT, Thoa LTB, Long NP, Trang NTH, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93:186-198H.
14. Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G. Informed consent: how much and what do patients understand? Am J Surg. 2009;198:420–35.
15. Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. Annu Rev Public Health. 2004;25:497–519.
16. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet Lond Engl. 2004;364:803–11.
17. Dein S, Bhui K. Issues concerning informed consent for medical research among non-westernized ethnic minority patients in the UK. J R Soc Med. 2005;98:354–6.
18. McCarthy DM, Waite KR, Curtis LM, Engel KG, Baker DW, Wolf MS. What did the doctor say? Health literacy and recall of medical instructions. Med Care. 2012;50:277–82.
19. Palazzani L, Macioce F, Daverio M, Ferro V, Persampieri L. New strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials. BioLaw J S. 2019;1:101–22.
20. Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries. J Med Ethics. 2012;38:356–65.
21. Garcia A, Garasic M, Ariano C, Cubillo M. Ethical issues concerning informed consent in translational / clinical research and vaccination. 2018. https://i-consentproject.eu/wp-content/uploads/2019/01/D1.4-Ethical-issues-concerning-informed-consent-in-translationalclinical-research-and-vaccination.pdf.
22. Dimitriou D, Rebera A, Cubillo M. Socio-cultural, psychological and behavioural perspectives toward informed consent process. 2018. https://i-consentproject.eu/wp-content/uploads/2019/01/D1.7-Sociocultural-psychological-and-behavioural-perspectives-towards-informed-consent-process.pdf.
23. O'Neill O. Accountability, trust and informed consent in medical practice and research. Clin Med Lond Engl. 2004;4:269–76.
24. Hugaas JV. An essay on the principle of informed consent versus the significance of trust for the subjects of biomedical research. Eubios J Asian Int Bioeth. 2002;12:65–70.
25. Bester J, Cole CM, Kodish E. The limits of informed consent for an overwhelmed patient: clinicians' role in protecting patients and preventing overwhelm. AMA J Ethics. 2016;18:869–86.
26. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. N Engl J Med. 2003;348:721–6.
27. Fons-Martínez J, Ferrer-Albero C, Russell R, Rodgers E, Glennie L, Díez-Domingo J. i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process. BioLaw J Riv BioDiritto Spec Issue 12019; 3–10.
28. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA. 2004;292:1593–601.
29. Dunn LB, Lindamer LA, Palmer BW, Schneiderman LJ, Jeste DV. Enhancing comprehension of consent for research in older patients with psychosis: a randomized study of a novel consent procedure. Am J Psychiatry. 2001;158:1911–3.
30. Campbell FA, Goldman BD, Boccia ML, Skinner M. The effect of format modifications and reading comprehension on recall of informed consent information by low-income parents: a comparison of print, video, and computer-based presentations. Patient Educ Couns. 2004;53:205–16.
31. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Med Ethics. 2013;14:28.
32. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

33. Rubin R. Addressing barriers to inclusion of pregnant women in clinical trials. JAMA. 2018;320:742–4.
34. Elkin EB, Pocus VH, Mushlin AI, Cigler T, Atoria CL, Polaneczky MM. Facilitating informed decisions about breast cancer screening: development and evaluation of a web-based decision aid for women in their 40s. BMC Med Inform Decis Mak. 2017;17:29.
35. Ryan RE, Prictor MJ, McLaughlin KJ, Hill SJ. Audio-visual presentation of information for informed consent for participation in clinical trials. Cochrane Database Syst Rev. 2008;CD003717.
36. Simon CM, Klein DW, Schartz HA. Interactive multimedia consent for biobanking: a randomized trial. Genet Med Off J Am Coll Med Genet. 2016;18:57–64.
37. Afolabi MO, McGrath N, D'Alessandro U, Kampmann B, Imoukhuede EB, Ravinetto RM, et al. A multimedia consent tool for research participants in the Gambia: a randomized controlled trial. Bull World Health Organ. 2015;93:320-328A.
38. Bossert S, Kahrass H, Heinemeyer U, Prokein J, Strech D. Participatory improvement of a template for informed consent documents in biobank research—study results and methodological reflections. BMC Med Ethics. 2017;18:78.
39. Sonne SC, Andrews JO, Gentilin SM, Oppenheimer S, Obeid J, Brady K, et al. Development and pilot testing of a video-assisted informed consent process. Contemp Clin Trials. 2013;36:25–31.
40. Hall EW, Sanchez TH, Stein AD, Stephenson R, Zlotorzynska M, Sineath RC, et al. Use of videos improves informed consent comprehension in web-based surveys among internet-using men who have sex with men: a randomized controlled trial. J Med Internet Res. 2017;19:e64.
41. Jacobsen PB, Wells KJ, Meade CD, Quinn GP, Lee J-H, Fulp WJ, et al. Effects of a brief multimedia psychoeducational intervention on the attitudes and interest of patients with cancer regarding clinical trial participation: a multicenter randomized controlled trial. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30:2516–21.
42. Hoffner B, Bauer-Wu S, Hitchcock-Bryan S, Powell M, Wolanski A, Joffe S. "Entering a clinical trial: is it right for you?": a randomized study of The Clinical Trials Video and its impact on the informed consent process. Cancer. 2012;118:1877–83.
43. Chapman N, McWhirter R, Armstrong MK, Fonseca R, Campbell JA, Nelson M, et al. Self-directed multimedia process for delivering participant informed consent. BMJ Open. 2020;10:e036977.
44. Jackson SM, Daverio M, Perez SL, Gesualdo F, Tozzi AE. Improving informed consent for novel vaccine research in a pediatric hospital setting using a blended research-designapproach. Front Pediatr. 2021;8:520803. https://doi.org/10.3389/fped.2020.520803.
45. Akhlaq A, McKinstry B, Muhammad KB, Sheikh A. Barriers and facilitators to health information exchange in low- and middle-income country settings: a systematic review. Health Policy Plan. 2016;31:1310–25.
46. Lenert LA, Ziegler J, Lee T, Unfred C, Mahmoud R. The risks of multimedia methods: effects of actor's race and gender on preferences for health states. J Am Med Inform Assoc JAMIA. 2000;7:177–85.
47. Thomas R, Deary A, Kaminski E, Stockton D, De Zueew N. Patients' preferences for video cassette recorded information: effect of age, sex and ethnic group. Eur J Cancer Care (Engl). 1999;8:83–6.
48. van Deursen AJ, van Dijk JA. The first-level digital divide shifts from inequalities in physical access to inequalities in material access. New Media Soc. 2019;21:354–75.

Publisher's Note

ANEXO 4: Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies.

BMC Medical Ethics

RESEARCH

Open Access

Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies

Jaime Fons-Martinez[1*], Cristina Ferrer-Albero[2] and Javier Diez-Domingo[1,2]

Abstract

Background: The H2020 i-CONSENT project has developed a set of guidelines that offer ethical recommendations and practical tools aimed at making the informed consent process in clinical studies more comprehensive, tailored, and inclusive. An analysis of the appropriateness of some of its novel recommendations was carried out by a group of experts representing different stakeholders.

Methods: An adaptation of the RAND/UCLA Appropriateness Method was used to assess the level of agreement on the recommendations among 14 representatives of different stakeholders, including patients, regulators, investigators, ethics experts, and the pharmaceutical industry. The process included two rounds of rating and a virtual meeting.

Results: Fifty-three recommendations were evaluated. After the first round, 34 recommendations were judged "appropriate"; 19 were judged "uncertain"; and none was judged "inappropriate". After the second round, 9 "uncertains" changed to "appropriate". All recommendations rated medians of 6.5–9 on a 1–9 scale (1 = "extremely inappropriate", 5 = "uncertain", 9 = "extremely appropriate"). The sections "General recommendations" and "Gender perspective during the consent process for clinical studies" showed the highest "uncertainty" rating. The four keys to improving the understanding of the ICP in clinical studies are to: (1) consider consent a two-way continuous interaction that begins at the first contact with the potential participant and continues until the end of the study; (2) improve investigators' communication skills; (3) co-create the information; and (4) use a layered approach, including information to compensate for the potential participant's possible lack of health literacy and a glossary of terms.

Conclusions: The RAND/UCLA method has demonstrated validity for assessing the appropriateness of recommendations in ethical guidelines. The recommendations of the i-CONSENT guidelines were mostly judged "appropriate" by all stakeholders involved in the informed consent process.

Keywords: Informed consent process, i-CONSENT, RAND/UCLA method, Ethical guidelines, Ethical recommendations

Background

The informed consent process (ICP) is one of the most important contributions of ethics in the field of clinical research. It ensures the autonomy of potential participants in their decision to participate in a study or to withdraw at any time without consequences.

*Correspondence: jaime.fons@fisabio.es
[1] Vaccine Research Area, Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Avda. de Catalunya, 21, 46020 Valencia, Spain
Full list of author information is available at the end of the article

The Belmont Report [1] identified three main ICP components: information, comprehension, and voluntariness. Fulfilling all these components is challenging. Information is a key element, in terms not only of its content but also its presentation. Proper understanding of this information must be ensured, so that an individual can make an informed decision, and the ICP must necessarily be free of coercion and undue influence, in order to ensure voluntariness.

Patient information and consent forms are increasingly long and difficult to understand. They are usually written in complex language (above the recommended grade 8 reading level) and often omit significant information [2, 3].Several studies have reported a lack of understanding of some content [4, 5], and no significant advances have been made in recent decades [6].

Despite the fact that informed consent, in addition to its informative purpose, is nowadays also used as the document that legally regulates the relationship between all parties involved in the study, some aspects must still be improved to ensure clear communication between participants and investigators. Proper information and efficient communication are mainstays for upholding the fundamental ethical principle of respect for the participant's autonomy.

Several guidelines and legal documents have been published on the consent process, addressing what informed consent is and should be, why is it important in clinical studies, the main procedures to follow during the ICP, and the minimum content to be covered. In accordance with these documents, the H2020 project i-CONSENT has developed a set of guidelines that provide ethical recommendations and practical tools that aim to make the ICP in clinical studies more comprehensive, tailored, and inclusive. The "Guidelines for Tailoring the Informed Consent Process in Clinical Studies" [7] (i-CONSENT guidelines) have been prepared from a review of the literature and based on the opinion of various experts (more information about the elaboration of the guidelines and the project is available on the project website [8] and in CORDIS [9]).

During the project, multiple literature reviews and systematic reviews were conducted to identify methods and strategies to improve informed consent, including the use of new technologies. Aspects of informed consent related to age and gender were also investigated, as well as socio-cultural perspectives on the notion of autonomy and other fundamental principles of informed consent. Ethical and legal issues related to the informed consent process were explored, including the review of the main international guidelines for medical research and the legal framework at national level of 6 countries (Austria, Spain, Italy, France, Germany, the UK) and the EU, in particular for women and minors involved in clinical research.

In addition, through different workshops and patient centered techniques the opinion of experts and representatives of the different stakeholders about different aspects of the informed consent process has been gathered. This information has allowed filling some of the gaps found in the literature and getting the perspectives of the main stakeholders about different aspects of the informed consent process.

All this input has been used in the development of the "Guidelines for Tailoring the Informed Consent Process in Clinical Studies". Most novel recommendations were extracted from these guidelines, and their appropriateness was analysed by a group of representatives from different stakeholders using an adaptation of the RAND/UCLA methodology. This study was performed to increase the quality of the recommendations included in the guidelines and made a very important contribution to the final guidelines. The validation of the guidelines by experts representing different stakeholders has been considered a key step prior to the final drafting of the guidelines.

Methods

An adaptation of the RAND/UCLA Appropriateness Method [10], identified by several authors as the best consensus method for developing guidelines and recommendations [11], was used to assess the level of agreement of representatives from different stakeholders on the recommendations for improving the understanding of the ICP in clinical studies, extracted from the i-CONSENT guidelines.

The expert panel comprised 14 representatives from different stakeholders, including patients, regulators, investigators, ethics experts, and the pharmaceutical industry.

Participants were selected according to their experience in relevant institutions or their prominence in the scientific literature. They were asked to give their own view, not that of their institutions.

The criteria follow to choose the participants were:

- Investigators: A review of authors from European organisations with articles in the field of informed consent was carried out, the authors considered most suitable in view of their published articles were selected and contacted by email.
- Patients: The European Patients' Academy on Therapeutic Innovation (EUPATI) was contacted and asked to forward information to their fellows and trainees so that those interested in participating could contact us. Several applications were received and those

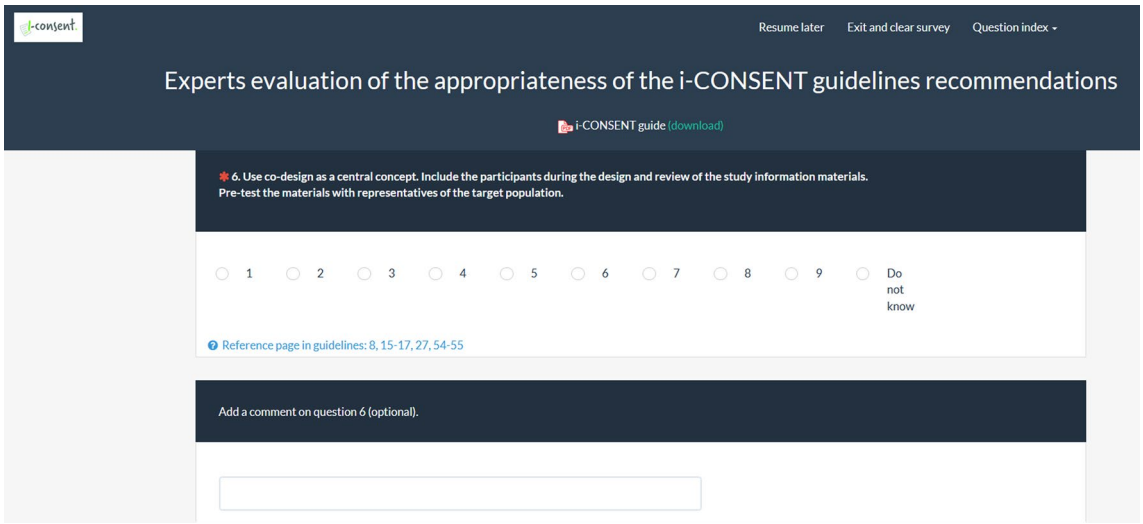


Fig. 1 Screenshot of the platform used to complete the survey

whose profiles were considered most interesting were chosen, including aspects such as membership of patient associations, chronic patient status or being a patient representative for other bodies (including regulatory bodies).

- Regulators: Representatives of national and international medicines agencies were contacted. Given the global pandemic situation, it was very difficult to get positive responses. Finally, the participation of a person from the EMA with a profile of interest to the study was secured.
- Ethics experts: Members of reputable ethics networks and bodies were selected. Two of the 3 experts included have an extensive scientific output on informed consent and research ethics; the third has a profile closer to regulation, which was considered optimal given the difficulties in contacting regulators.
- Pharmaceutical industry: Informed consent experts were selected from the pharmaceutical industry, including experts in this field from the Transcelerate Biopharma initiative, through GSK and EFPIA members.

A set of 30 recommendations, 53 including the sub-recommendations, were divided into 10 sections, including the 5 ICP steps specified in the i-CONSENT guidelines, as follows:

- General recommendations
- Recommendations for the preparation of information
- Step 1: First contact with the potential participant
- Step 2: Provision of information
- Step 3: Discussion and decision-making
- Step 4: Intervention and follow-up
- Step 5: End of the study
- The gender perspective during the consent process for clinical studies
- ICP in clinical studies involving minors
- ICP in clinical studies involving people from different cultural and religious backgrounds

The experts were asked to rate the appropriateness of each recommendation from 1 to 9, where 1 is "extremely inappropriate" and 9 is "extremely appropriate" (appropriateness scale: 1 = "extremely inappropriate", 5 = "uncertain", 9 = "extremely appropriate"). A "Do not know" option was added, for use only when the question was outside the respondent's field of expertise. Ratings were made with an average potential participant and an average clinical study in mind, focusing on the recommendation's effectiveness, without considering cost implications. The survey was completed on an electronic platform (Fig. 1).

The process included two rounds of rating, as follows:

1. Fourteen experts agreed to participate after receiving a detailed explanation of the RAND process.
2. First round of rating: panellist received the link and instructions on how to complete the survey. They were given 3 weeks to complete the survey and submit their responses.
3. A Personalised Panellist Rating Sheet (PPRS) was prepared and sent to each panellist. It included the frequency of responses for each recommendation, the median, the mean absolute deviation from the median, their own response, and the comments

6. Use co-design as a central concept. Include the participants during the design and review of the study information materials. Pre-test the materials with representatives of the target population

Options (Appropriateness)	1	2	3	4	5	6	7	8	9	Don't Know
Times selected	0	0	0	0	0	0	3	1	10	0

Median: 9

Mean absolute deviation from the median: 0,5

Your answer: 9

Comments:

- In particular expert patient able to represent the needs of community and not only the individual need
- Not just for the information materials but throughout the whole project
- Patient's organizations could also review the appropriateness of the materials to the target population.
- However - recommend not to co-develop the information materials with prospective participants as it may introduce several kinds of bias. Work with representatives from the target population who will not join the study

Fig. 2 Example of the information about a recommendation in the PPRS

included by the panellists on each recommendation (see example in Fig. 2).

4. A virtual meeting of the panel of experts with a second round of rating was held on an online platform. The aim was to discuss the recommendations that had not achieved clear agreement after the first round of rating. The aim of the virtual meeting was not to force the panel to reach consensus and this was indicated to the panellists. Therefore, the aim was, on the one hand, for the panellists to be able to state their positions and express their doubts or suggestions; on the other hand, for the i-CONSENT team to clarify the reason and meaning of each recommendation, thus facilitated the correct understanding of the recommendations and ensured that all panellists evaluated the same thing. The virtual meeting allowed the different points of view to be presented, clarified and discussed. After discussing the recommendations, a second round of rating took place. Each panellist had access to their answers from the first round for this second round.

Levels of appropriateness and agreement were defined on the basis of the recommendations included in "The RAND/UCLA Appropriateness Method User's Manual" [10].

Appropriateness levels were determined by the median of the panel and the presence (or absence) of agreement. The original definition was modified to a more restrictive position, taking into consideration a lack of agreement (rather than the existence of disagreement) sufficient to consider a recommendation as "uncertain". Median ratings falling exactly between the 3-point boundaries (3.5 and 6.5) were included in the higher appropriateness category.

Levels of appropriateness:

- "Appropriate": panel median of 6.5–9, with agreement
- "Uncertain": panel median of 3.5–6 OR any median without agreement
- "Inappropriate": panel median of 1–3, with agreement

The definition of agreement or disagreement depended on the panel size and the distribution of the panellist ratings on the 3-point regions (Table 1). Because a "Don't know" category of response was included, the panel size was calculated for each recommendation including only responses with a rating of 1–9.

Table 1 Definition of agreement and disagreement among panellists for different panel sizes

Panel size	Disagreement	Agreement
	Number of panellists rating at each extreme (1–3 and 7–9)	Number of panellists rating outside the 3-point region containing the median (1–3; 4–6; 7–9)
From 8 to 10	3 or more	2 or less
From 11 to13	4 or more	3 or less
From 14 to 16	5 or more	4 or less

Source "The RAND/UCLA Appropriateness Method User's Manual" [10]

Results

All 14 panellists (10 women, 4 men) from 12 different countries (10 European, 2 non-European) representing 5 stakeholders[1] (5 patient representatives; 1 regulator; 3 investigators; 3 ethics experts; 2 pharmaceutical industry representatives) submitted the survey on time during the 2 rounds of rating and all panellists attended the virtual meeting.

After the first round, 34 recommendations were considered "appropriate"; 19 were considered "uncertain"; 0 recommendations were considered "inappropriate". The median of 52 recommendations was in the "appropriate" range and 1 was in the "uncertain" range.

The 19 recommendations with an "uncertain" level of appropriateness were discussed in the virtual meeting. The recommendations discussed were:

General Recommendations

Recommendation (Rec.) 2. *Feedback from participants:*

- **Rec. 2.2**. Feedback should be obtained at all stages:

  On the experience before starting the study (obtained during the first month of participation).
  On the experience during the study (obtained during the trial).
  On the experience at the end of the study (obtained at the last visit).

- **Rec. 2.3**. Conduct a debriefing session with your team about the consent process using this information:

  A session held after the study may help to improve the consent process in future studies.
  A session held during the study may also help to improve the process of the current study.

- **Rec. 4.** Digital and health literacy:

  Rec. 4.1. Train your participants to improve their digital and health literacy.
  Rec. 4.3. Use links to "further information".
  Rec. 4.4. Provide participants with information on how to detect fake news and unreliable sources.

Recommendations for preparing information

- **Rec. 5.** Use interdisciplinary quantitative and qualitative methodologies to define your study population, interests, and needs. It may be useful to:

  review the available literature on the target population (e.g., systematic or narrative literature review);
  ask the target population directly (e.g. interviews, surveys, Design Thinking);
  seek advice from experts (key informant interviews, brainstorming, etc.);
  observe the target population; and/or
  analyse their interactions on social media and blogs.

- **Rec. 11.** Provide references to reliable sources of information.
- **Rec. 12.** If using placebo, include a short description of the placebo effect (positive and negative).

Step 1: First contact with the potential participant

Rec. 13. Due to the growing use of digital technology among the population and the appearance of decentralised clinical trials, consider:

Rec. 13.1. Use of different channels to advertise the study:

Social media
Email

[1] Some panellists belonged to more than one group but were included in the one most representative for them.

Step 3: Discussion and decision-making

Rec. 18. Check that potential participants have understood all study information by:

Interview: Teach-back or teach-to-goal methods can be helpful.
Questionnaires, such as the Quality of Informed Consent (QuIC), Deaconess Informed Consent Comprehension Test (DICCT), or the Brief Informed Consent Evaluation Protocol (BICEP).

Step 5: End of the study

- **Rec. 23.** Summary of results for laypersons:

Rec. 23.2. Consider involving participants in the development and review of the summary.

The gender perspective during the consent process for clinical studies

- **Rec. 25**. Adapt consent information by gender only when the strategy or study is directed at a single sex group.
- **Rec. 26.** In the case of women from different cultural backgrounds, consider using a cultural mediator with a gendered approach in order to bridge communication gaps.
- **Rec. 27.** Connect with the participant:

Rec. 27.1. In research of a more sensitive nature (e.g. trials of vaccines against sexually transmitted diseases), it may be beneficial if the investigator in contact with the potential participant is of the same sex
Rec. 27.2. The major focus should be on connecting with the individual participant, rather than making gender-based assumptions

The ICP in clinical studies involving minors

- **Rec. 29.** Information for children:

Rec. 29.1. Choose the information for the child on the basis of the minor's level of maturity and their capacity of comprehension, not only on their age.
Rec. 29.5. Assess the minor's capacity and understanding through:

Dialogue with the investigator (using a teach-back method).
Multiple choice questionnaires and/or open questions, such as MacCAT-CR test modified for children and adolescents.

All 53 recommendations were re-rated during the meeting. Results of second-round ratings are shown in Additional file 1.

After the second round, 42 recommendations were considered "appropriate" [12 of them were rated by all 14 panellists with scores between 7 and 9], 11 as "uncertain" (all of them with medians equals or above 6.5 but with disagreement), and none were considered "inappropriate". Additional information in Additional file 1 lists the 53 recommendations and their results in the second round.

"General recommendations" and "Gender perspective during the consent process for clinical studies" were the two sections with a higher percentage of recommendations rated "uncertain". Outside of these two sections, recommendations on how to assess understanding of informed consent and assent were the most questioned by the panellists.

Discussion

Fifty-three recommendations were extracted and evaluated by the experts in this study. Most of the recommendations were considered "appropriate" and only a few changes were suggested. The modification of "appropriateness" to a more restrictive level resulted in a greater number of recommendations with the result "uncertain". This was very positive as it permitted a more fruitful discussion during the virtual meeting. It should be noted that on the original scale of appropriateness levels, all the recommendations evaluated would have been rated as "appropriate" after the two rounds.

The outcome of the virtual meeting was a better understanding of the panellists' point of view, leading to the modification of some recommendations towards a more consensual content and wording. It was also an opportunity to explain the i-CONSENT rationale behind each recommendation, to clarify any doubts, and to allow all the experts to share their opinion on each recommendation. This approach benefitted the second-round evaluation, which better reflects the experts' opinion.

It is also important to mention that none of the recommendations evaluated had "inappropriate" as result or had significant disagreement among the panellists, in which case they would have been removed from the guidelines. Furthermore, since there is no indication that any of the recommendations with the result "uncertain" were harmful (all of them had medians in the

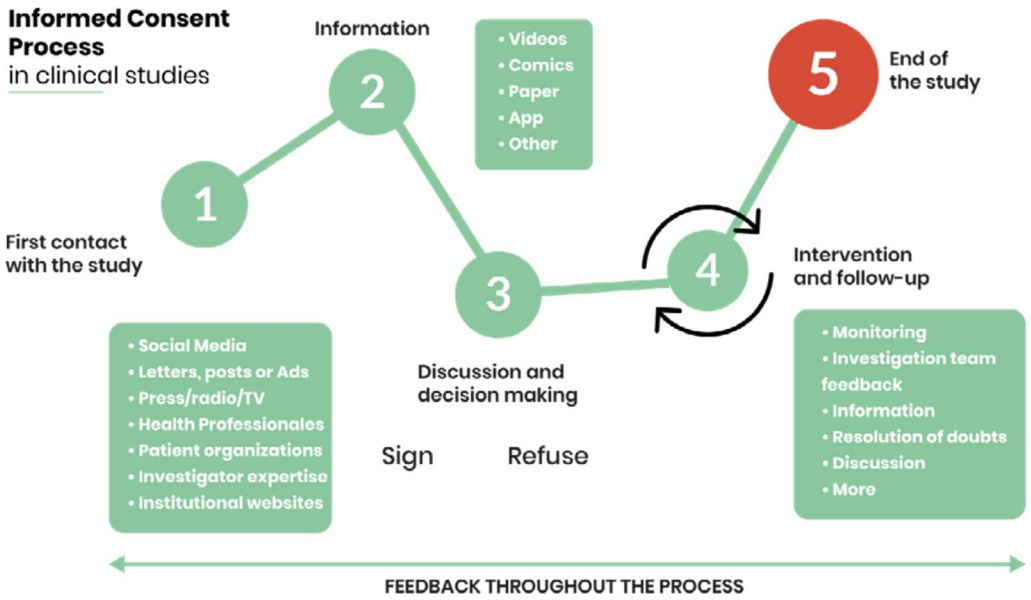


Fig. 3 The informed consent process in clinical studies. *Source:* Guidelines for Tailoring the Informed Consent Process in Clinical Studies (7) (2021)

"appropriate" range and were proposed as a result of the research conducted during the project), they have been maintained in the guidelines, albeit in most cases with modifications derived from this study (Additional file 2).

The composition of the panel, with overrepresentation of patient representatives and women, was especially suitable for the objectives of the study, as two of the main objectives of the guidelines aim to put study participants in the centre of the process and to include a gender perspective. It is also important to note that most of the patient representatives were also investigators. Furthermore, due to COVID-19 pandemic, the in-person meeting was conducted remotely. The impact of these factors on the final results was thought to be low.

The following discussion focuses mainly on recommendations with the result "uncertain" after the first round of scoring.

IC as a continuous communication process

The recommendation rated highest in the overall survey was to consider informed consent as a "two-way continuous communication process that begins at first contact with the potential participant and continues until the end of the study".

The ICP described in the i-CONSENT guidelines is a five-step process (Fig. 3). During this process, continuous feedback and communication between the potential or current participant and the research team is essential.

This "first contact", as described in the i-CONSENT guidelines, aims to raise awareness of the study and provide essential study information before the recruitment process begins.

The panellists found it appropriate to consider the use of different channels to advertise the study, including social media and websites, in addition to the traditional routes. Even so, they highlighted the need to consider aspects of digital poverty and how the use of these channels actively excludes some pockets of society. The experts were also very cautious about recommending the use of email to reach out to potential participants. Recommendation 13 was reformulated after discussion to add some clarification and to remove any mention of decentralized clinical trials.

It is important to note that the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) [12] highlight the importance of understanding the implications of recruiting patients to research via social media.

Panellists agreed to recommend the inclusion of the following information during this first contact:

- The purpose of the research, the importance of the study, and expected duration;
- The target population with some inclusion/exclusion criteria (e.g., pregnant women between 18–40 years old);
- A brief description of the relevant study procedures (e.g., a routine blood sample); and

- The contact person at the study site.

A recommendation to provide the potential participant with all relevant information about the study (step 2) before the discussion with the investigator (step 3) was also considered appropriate, in order to ensure that they have had sufficient time to think about it and to prepare any questions.

The discussion between the potential participant and the investigator is clearly seen as a fundamental step of the ICP. The i-CONSENT project, however, strongly recommends separating both events (information and dialogue) during the process, because some potential participants make the decision to participate based solely on this interaction, without fully reading the patient information sheet (PIS) to the end. Traceability of dialogue is very difficult, and it is impossible to guarantee that all relevant information about the study has been delivered during the discussion.

Furthermore, it was considered appropriate that the participant be assured access to the information used during the ICP and knows how to access it throughout the study and for the period established by law.

The panellists also agreed on the importance of obtaining participants' feedback on the ICP but they were unsure about how to obtain it (how often, when, how). The i-CONSENT project advocates obtaining feedback from participants to make the ICP more dynamic and responsive over time, adjusting it to the needs and preferences of the participants. The i-CONSENT also highlights the use of feedback tools, such as the Study Participant Feedback Questionnaire Toolkit [13] developed by Transcelerate Biopharma. The i-CONSENT similarly recommends obtaining feedback at different moments during the study: after signing the consent, during the intervention, and at the end of the study. Although none of the panellists advised against obtaining feedback at these three timepoints, and the majority of panellists were in favour of the concept, there was no agreement on the appropriateness of this recommendation, since some respondents considered that this could overburden investigators and/or participants.

Health and digital literacy

Several studies identify health literacy as an important determinant of a patient's capacity to provide fully informed consent [14, 15], and the i-CONSENT project sees the consent process as an opportunity to improve the health literacy of participants.

Panellists recognise the importance of health literacy but, in their opinion, it is not the duty of the research team to train participants in health and digital literacy or on how to detect fake news and unreliable sources. Some believed that these recommendations place an excessive burden on investigators.

Panellists believed that the emphasis should be on adapting the information to the target population's preferences and needs, instead of adapting the population to the information. In this respect, one of the panellists stated: "I do not agree that the ICP should train participants in health literacy. The ambition for study teams MUST be to adjust information to the level(s) of participants, who might otherwise feel unsure or disrespected in their own right."

Another idea highlighted by the panellists was the importance of creating information that does not require any further consultation, and that is easy for everyone to understand. In fact, there was no agreement on providing references or links to reliable sources of information.

Three recommendations considered appropriate by the panellists on this topic were to:

- Design the information to complete a possible lack of health literacy on the part of the potential participant.
- Use a glossary of terms to explain complex concepts.
- Use a layered approach for introducing study information, presenting the basic information in the general level and more specific messages in sub-layers. When using a document format (paper or pdf), these layers must be easily identifiable: the first layer will be in the main body and the sub-layers can come in a different format, such as in boxes or in different colours, or they can be presented in annexes.

Co-creation as a key idea

Co-creation was highlighted as a key intervention to increase the quality and understanding of the ICP, including the development of consent information. All panellists believed it was appropriate to recommend the "use of co-design as a central concept. Include participants during the design and review of the study information. Pre-test the information with representatives of the target population". This is in line with the findings of a previous study conducted with representatives of patient groups in the framework of the i-CONSENT project [16].

Co-creation is important when producing a PIS, and it is equally important to summarize results, decision aids or any material about health information, such as information leaflets, in plain language. This took on particular importance when recommendation 23.2 was discussed: this recommendation was considered too weak because the recommendation to involve participants in the development and review of the summary was to be "considered" rather than a "must". Therefore, the

recommendation was reformulated as "Involve participants in the development and review of the summary of results".

The panellists believe that it is appropriate to recommend co-design as a central concept and to use quantitative and qualitative interdisciplinary methodologies to involve and obtain insights from the target population. This strategy reinforces the proposal made by Jackson et al. to use a participatory and mixed methods approach to design informed consent in a way that best suits the needs of participants [17].

Tailoring the informed consent to potential participant preferences and needs

Usually during the ICP, patient information is only tailored to individual needs during in-person interactions. Normally, information materials are prepared without taking into account the preferences and needs of the target population.

Using a participatory and mixed method approach to develop informed consent will help identify the preferences and needs of the target population, including preferences regarding formats for presenting the information or the channels for contacting the research team.

Even so, as individual needs may differ from the general preferences of the target population, offering different possibilities during the ICP will help tailor it to the individual.

In this regard, most of the panellists felt that it was appropriate to offer potential participants a choice of more than one format for receiving information, and to provide different channels and formats for communicating with the research team.

As mentioned in the section on health and digital literacy, it is important to consider the benefit of presenting the information using a layered approach (especially if using a website). This approach will let the individual delve into the information they find most relevant or explore the explanations they need for better understanding.

Use of technical and methodological innovations

The use of digital technologies during the ICP is increasing. Several studies have measured the impact of interventions using multimedia, audio–video, or gamification to provide information to patients or potential participants [18, 19].

Most panellists considered it appropriate to recommend the use of technical and methodological innovations during the ICP to facilitate the participant experience, including the use of new technologies and formats to deliver information (hyperlinked website, video, storytelling, comics, mobile applications). It is important to note that the adequacy of this approach should always be taken into account from a social, methodological, legal, and ethical point of view.

Prepare inclusive information

According to the principle of justice and to ensure that the potential participant feels identified with the information provided, it is very important to prepare inclusive information and to implement an intercultural approach and a gender perspective.

The panellists believed that it is very appropriate to recommend procedures that incorporate a sensitive intercultural approach, empathizing with and being sensitive to the preferences and needs of people from different cultures, and adapting the consent process to their requirements as far as possible. Information should be provided in an easy-to-understand and culturally appropriate language and the participation of trained cross-cultural professionals in the study should be encouraged. It is also important to be aware that key concepts can be understood differently.

Literature on the gender perspective in the consent process is scant, and this is a controversial issue. Several studies exploring the ICP as a communication process have identified gender differences in this interaction. Even so, most authors agree that there are more common characteristics than differences, and that the differences identified are not categorical. Most studies that analysed differences in the understanding of informed consent in clinical trials by gender found no differences [4, 6, 20]. Indeed, the few studies that identified differences mostly found a better understanding by women [21–24]. Some studies also found that women were more inclined to read the entire PIS [25].

The panellists highlighted the importance of applying a gender perspective during the consent process, taking into account the influence of gender on health needs and concerns. This concern is in line with that expressed by the European Commission in the H2020 call "SwafS-17–2016—The ethics of informed consent in novel treatment including a gender perspective".

The consent process must be conducted without reinforcing stereotypes. Using one PIS for men and another for women in the same study is difficult to justify and unacceptable in most cases. The best way to adapt informed consent to the target population is to take that population into account when designing the information via a process of co-creation. Moreover, in-person discussion will be essential to adapt the consent process to the particular characteristics of the potential participant, connecting with the individual without making gender-based assumptions.

Two actions that seemed to be beneficial in applying a gender perspective, but that failed to achieve agreement during the study, were:

- When the study is directed at a single sex group, it can be useful to take into account communication and eye-tracking differences when designing the materials.
- In research of a more sensitive nature (e.g., trials of vaccines against sexually transmitted diseases) it may be beneficial if the investigator in contact with the potential participant is of the same sex.

Assessing understanding of information

Recommendations 18 and 29 highlighted the importance of the communication skills of the investigator. Panellists stated that the potential participant's understanding has to be achieved through natural conversation. The experts were very critical of the use of questionnaires (especially with MacCAT) or the teach-back method. These, in their opinion, feel artificial and make the potential participant feel as if they are in an exam. However, given that the scientific literature has repeatedly pointed out the usefulness of techniques such as the teach-back method or questionnaires (including self-completion) to assess the level of understanding of potential participants [5, 19, 26, 27], we believe that while the best option is to have investigators with good communication skills that do not need to use these components, they can be a useful tool during verbal discussion at certain times.

Defining how to assess understanding is another important question that emerged during the discussion. The initial proposal for recommendation 18 was to verify that potential participants have understood "all" the information about the study, but this was considered unrealistic and unnecessary in most studies, and a more appropriate recommendation would be to verify that potential participants have understood "all relevant" information about the study. The information considered as relevant must be defined during the co-creation of the information, taking into account both perspectives (investigator/sponsor and potential participants).

In addition to providing clear and complete information, ensuring its understanding and replying to the doubts the potential participant, the panellists believe it is appropriate to recommend the use of decision-making tools to facilitate the process.

Participant involvement at the end of the study

Participants should be informed at the end of the study about the results, and they should also be included in the early phases of disseminating the results.

A "thank you letter" is a good way of thanking the participant for their participation in the study and, if possible, giving a preview of the results and instructions on how to access the summary of results when it is ready.

Providing a summary of results is considered appropriate for all studies, not only clinical trials; participants should be involved in producing and reviewing the summary (as mentioned above). Other formats, including written reports, may be considered for the summary and the one that best suits the characteristics of the target population must be selected.

Conclusion

The RAND/UCLA method has demonstrated validity for assessing the appropriateness of recommendations in ethical guidelines and can be used to obtain quantitative and qualitative information from panellists. Both rounds of rating provide very valuable information: the first round is very useful for detecting the recommendations for which there is already consensus regarding their status as "appropriate" or "inappropriate". This made for a more productive meeting and focused the discussion on the recommendations rated as "uncertain" or without consensus. The changes between the first and second round are consistent with the initial ratings and the discussion. The inclusion of boxes in which to add comments on each recommendation during the rating rounds was very useful for a better understanding of the panellists' point of view and for making a qualitative interpretation of the results.

Most of the recommendations drawn from the i-CONSENT guidelines were considered "appropriate" by the panellists, and none was considered "inappropriate". Only a few were rated as "uncertain" and this was always because of a lack of agreement. Medians for all recommendations fell between 6.5 and 9. Some "uncertain" recommendations have been reformulated or partially changed taking into account experts' opinion (Additional file 2).

The four key aspects for improving the understanding of the ICP in clinical studies are:

- To consider consent a continuous two-way communication process that begins at the time of first contact with the potential participant, and continues until the end of the study;
- To improve investigators' communication skills;
- To co-create information materials; and
- To use a layered approach, including information to compensate for a possible lack of health literacy on the part of the potential participant and a glossary of terms.

In addition to providing comprehensible information, it is essential to assess that all relevant information has been properly understood. It is recommended that understanding be assessed in a natural conversation and that the questions asked by the potential participant and their body language are evaluated by a well-trained researcher. This is preferable to the use of tools, such as the teach-back method or surveys, that can seem artificial and make people to feel as if they are in an exam.

Abbreviations

ICP: Informed consent process; PIS: Patient information sheet; PPRS: Personalised panellist rating sheet; Rec.: Recommendation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12910-021-00708-1.

Additional file 1. List of recommendations rated by the panellists and results after round 2.

Additional file 2. Recommendations reformulated after 2 rounds of rating and virtual discussion.

Acknowledgements

We would like to express our gratitude to all the experts who participated in the evaluation of the recommendations.

Authors' contributions

JFM and JDD made substantial contributions to the conception and design of the work. JFM lead and moderated the RAND/UCLA study, analysed the data and drafted the article. JDD participated in the development of the RAND/UCLA study, review, and suggested modifications to the manuscript. CFA supported the RAND/UCLA and made substantial improvement to the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded by Horizon 2020 SwafS-17–2016 GA n.741856 and conducted under the framework of the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective (i-CONSENT)".

Availability of data and materials

The anonymized data are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Consent to participate was requested when panellists were first contacted and a related question was included at the beginning of the questionnaire. Informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki. The i-CONSENT project was approved by the Ethics Committee of Clinical Research of the Dirección General de Salud Pública and Centro Superior de Investigación en Salud Pública.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Vaccine Research Area, Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Avda. de Catalunya, 21, 46020 Valencia, Spain. [2]Facultad de Medicina y Ciencias de la Salud, Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain.

Received: 26 March 2021 Accepted: 23 September 2021
Published online: 13 October 2021

References

1. Office for Human Research Protections (OHRP). The Belmont Report Washington: U.S. Department of Health & Human Services; [updated 2018 January 15; cited 2020 August 17]. Available from: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.
2. Beardsley E, Jefford M, Mileshkin L. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? J Clin Oncol. 2007;25(9):e13–4.
3. Villamañán E, Ruano M, Fernández-de Uzquiano E, Lavilla P, González D, Freire M, et al. Informed consent in clinical research; Do patients understand what they have signed? Farm Hosp. 2016;40(3):209–18.
4. Alexa-Stratulat T, Neagu M, Neagu AI, Alexa ID, Ioan BG. Consent for participating in clinical trials - is it really informed? Dev World Bioeth. 2018;18(3):299–306.
5. Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G. Informed consent: how much and what do patients understand? Am J Surg. 2009;198(3):420–35.
6. Tam NT, Huy NT, le Thoa TB, Long NP, Trang NT, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93(3):186–98.
7. i-CONSENT Consortium. Guidelines for Tailoring the Informed Consent Process in Clinical Studies. Spain: FISABIO. Generalitat Valenciana. 2021. https://doi.org/10.5281/zenodo.4563938.
8. Improving the guidelines for Informed Consent. i-CONSENT [cited 2020 August 25]. Available from: https://i-consentproject.eu/.
9. European Commission. CORDIS. EU research results. Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective [cited 2020 August 25]. Available from: https://cordis.europa.eu/project/id/741856.
10. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The Rand/UCLA appropriateness method user's manual. Santa Monica, CA: RAND Corporation; 2001.
11. Masdeu Ávila C. Metodología Delphi en salud. Hipertens riesgo vasc. 2015;32(Supl 1):12–6.
12. Donegan K, Ovelgonne H, Flores G, Fuglerud P, Georgescu A. Social Media and M-Health Data. Heads of Medicines Agencies. European Medicines Agency.
13. Transcelerate Biopharma. Study Participant Feedback Questionnaire Toolkit [cited 2020 August 25]. Available from: https://transceleratebiopharmainc.com/patientexperience/study-participant-feedback-questionnaire.
14. Sherlock A, Brownie S. Patients' recollection and understanding of informed consent: a literature review. ANZ J Surg. 2014;84(4):207–10.
15. Perrenoud B, Velonaki VS, Bodenmann P, Ramelet AS. The effectiveness of health literacy interventions on the informed consent process of health care users: a systematic review protocol. JBI Database System Rev Implement Rep. 2015;13(10):82–94.
16. Fons-Martínez J, Ferrer-Albero C, Russell R, Rodgers E, Glennie L, Díez-Domingo J. i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process. BioLaw Journal. 2019(Special Issue):3–10.
17. Jackson SM, Daverio M, Perez SL, Gesualdo F, Tozzi AE. Improving Informed Consent for Novel Vaccine Research in a Pediatric Hospital Setting Using a Blended Research-Design Approach. Front Pediatr. 2020;8:520803.

18. Gesualdo F, Daverio M, Palazzani L, Dimitriou D, Diez-Domingo J, Fons-Martinez J, et al. Digital tools in the informed consent process: a systematic review. BMC Med Ethics. 2021;22(1):18.
19. Glaser J, Nouri S, Fernandez A, Sudore RL, Schillinger D, Klein-Fedyshin M, et al. Interventions to improve patient comprehension in informed consent for medical and surgical procedures: an updated systematic review. Med Decis Making. 2020;40(2):119–43.
20. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA. 2004;292(13):1593–601.
21. Paris A, Deygas B, Cornu C, Thalamas C, Maison P, Duale C, et al. Improved informed consent documents for biomedical research do not increase patients' understanding but reduce enrolment: a study in real settings. Br J Clin Pharmacol. 2015;80(5):1010–20.
22. Raich PC, Plomer KD, Coyne CA. Literacy, comprehension, and informed consent in clinical research. Cancer Invest. 2001;19(4):437–45.
23. Morrow G, Gootnick J, Schmale A. A simple technique for increasing cancer patients knowledge of informed consent to treatment. Cancer. 1978;42(2):793–9.
24. Klima J, Fitzgerald-Butt SM, Kelleher KJ, Chisolm DJ, Comstock RD, Ferketich AK, et al. Understanding of informed consent by parents of children enrolled in a genetic biobank. Genet Med. 2014;16(2):141–8.
25. Fons-Martínez J, Diez-Domingo J, Calvo Rigual F, Ferrer-Albero C, Cubillo Diaz-Valdes M. Deliverable D1.2: Report on gender and age-related issues associated with the acquisition of informed consent. 2017: i-CONSENT project [cited 2020 August 25]. Available from: https://cordis.europa.eu/project/id/741856/results
26. Atal S, Dunne F. Assessment of the understanding of informed consent including participants' experiences, and generation of a supplemental consent decision aid for Gestational Diabetes Mellitus (GDM) research. HRB Open Res. 2018;1:12. https://doi.org/10.12688/hrbopenres.12811.1.
27. Kadam RA. Informed consent process: A step further towards making it meaningful! Perspect Clin Res. 2017;8(3):107–12. https://doi.org/10.4103/picr.PICR_147_16.

Publisher's Note

ANEXO 5: Keys to improving the informed consent process in research: Highlights of the i-CONSENT project.

DOI: 10.1111/hex.13427

EDITORIAL

WILEY

Keys to improving the informed consent process in research: Highlights of the i-CONSENT project

The ethical and legal governance of all aspects of informed consent in research is becoming increasingly extensive and complex. Instead of a single directive, informed consent is governed by a series of international rules applied to biomedical research, clinical trials and biobanks, while various ethical guidelines for research have been published by different international bodies.

Informed consent is an essential part of any research involving humans, but the array of available guidelines can complicate the informed consent process for sponsors, researchers and participants. Sponsors, in particular, find it difficult to adapt the informed consent process to the characteristics of the participants. Moreover, because of the length and complexity of informed consents, some participants may misconstrue key points[1] and agree to participate in a trial that they do not fully understand. In these cases, the decision on their participation is mainly based on discussions with the researcher, which lacks traceability.

In 2017, the European Commission responded to the need to improve the informed consent process and informed consent readability by launching the project 'Improving the guidelines of informed consent, including vulnerable populations, under a gender perspective (i-CONSENT)' (Grant Agreement 741856).

The ethical and legal framework of the i-CONSENT project was later supplemented with the publication *'Guidelines for Tailoring the Informed Consent Process in Clinical Studies'*, which includes more specific guidelines for developing evidence-based patient information materials that take into consideration gender, multiculturalism and the vulnerable populations that are usually underrepresented in research. The guidelines also provide a series of easy-to-read and easy-to-use fact sheets and tools that complement the main document, highlight the importance of various aspects of the informed consent process and offer recommendations on how to implement best practices. These fact sheets include, among others, how to present study information in consent materials; how to assess participant understanding; how to establish an appropriate relationship between the investigator and the participant during the process; and how to address some of the major ethical challenges that may arise in pandemic situations such as COVID-19.

This article summarizes the key aspects of the informed consent process from the perspective of the i-CONSENT project.

During the development of the guidelines, multiple reviews of the scientific literature and ethical and legal texts were carried out, as well as workshops, seminars and surveys that allowed us to obtain the opinions on different aspects of informed consent of different people, including representatives of patients and potential participants in clinical studies, experts in legislation, experts in ethics, members of ethics committees, investigators, members of the pharmaceutical industry, legislators and cultural mediators.

The above-mentioned guidelines and the rest of the project deliverables can be accessed from the CORDIS platform.[2]

1 | INFORMED CONSENT AS A PROCESS

The main paradigm—an approach suggested earlier by the Council for International Organizations of Medical Sciences—is to view informed consent as a process rather than a bureaucratic procedure aimed merely at obtaining a signature on a document. This guideline identifies and describes five informed consent process phases that are set in motion the moment a potential participant receives information about a particular study and end when the study is completed (Figure 1). It also guides the researcher through each phase of the informed consent process and ensures the autonomy of the potential participant in each phase.

The guidelines, which supplement existing informed consent documentation, introduce novel recommendations in three directions: the adaptation of the informed consent process to potential participants; the improvement of the participant's experience; and the use of new tools to guide the informed consent process. The perspective of potential participants in clinical research was taken into account in the development and design of the guidelines.[2]

2 | ADAPTATION OF THE INFORMED CONSENT PROCESS TO POTENTIAL PARTICIPANTS

The first recommendation is to adapt the informed consent process to the preferences, interests and needs of the potential participant, focusing on the target population throughout the research process.

Representatives of the target population should be involved in all steps, including designing and cocreating the document, implementing the informed consent process and receiving subsequent feedback that can improve the initial process. Design Thinking methodology is recommended to tailor the information to the audience.

This new approach involves two-way, seamless interaction with participants[3] that allows the researcher to detect and clarify concepts that are likely to be misunderstood, especially by people with low health literacy, and avoids overwhelming potential participants with excessive information. The strategy of providing information in layers allows participants to decide for themselves how much information they receive about a research study.

3 | PRESENTING INFORMATION IN DIFFERENT FORMATS

In today's world, reading and learning habits have changed, and written texts now include other elements such as hyperlinks, multimedia, images and infographics. The informed consent should be tailored to social changes that facilitate understanding and should be presented in different formats, which may or may not be combined with new technologies.[4] The participants, depending on their personal characteristics, may choose the format that best suits their preferences and needs.

4 | NEW TOOLS TO IMPROVE COMMUNICATION

The guidelines include practical tools and checklists that help users meet regulatory and stakeholder requirements and identify and review all key aspects that must be covered by the informed consent process. This approach will improve understanding and satisfy the needs and preferences of potential participants.

The guidelines also include 14 fact sheets and six tools that highlight the different issues addressed in the informed consent process and offer recommendations on how to implement best practices. The fact sheets explore in greater depth topics such as presenting the informed consent, evaluating comprehension, information and using decision-making tools. The tools address matters that are not strictly related to the informed consent process, but that are useful for improving the process, for example, communication skills, writing a thank you letter or methods for incorporating the perspective of the participants.

5 | GUIDELINES' VALIDATION

The recommendations put forward have been validated at several levels.

The RAND/UCLA method for validating clinical guidelines was used to analyse and validate the appropriateness of the main recommendations, particularly the most innovative aspects.[5] The evaluation panel comprised patient representatives, investigators, experts in ethics, pharmaceutical industry representatives and regulators, all of them external to the project. Fifty-three recommendations were evaluated. Of these, 43 were considered 'appropriate'; 10 were considered 'uncertain'; and none were considered 'inappropriate'. All recommendations rated medians of 6.5–9 on a 1–9 scale (1 = 'extremely inappropriate', 5 = 'uncertain', 9 = 'extremely appropriate'). Discrepancies were discussed by the expert panel, and some recommendations were adapted.

To validate the recommendations in a target population, three pilot consent forms were designed for hypothetical clinical trials with vaccines, one for children, one for pregnant women and one for adults, in three culturally different countries. Since these were not real clinical trials, only the recommendations for drafting information (step 2 of the Informed Consent Process; see Figure 1) were taken into consideration in the informed consent process. These recommendations include the involvement of potential participants in the design and piloting of consent materials. In two of the three hypothetical clinical trials, materials were cocreated with potential participants through design thinking sessions. In the third, a survey was conducted to learn the needs and preferences of potential participants. All three materials were piloted with potential participants.

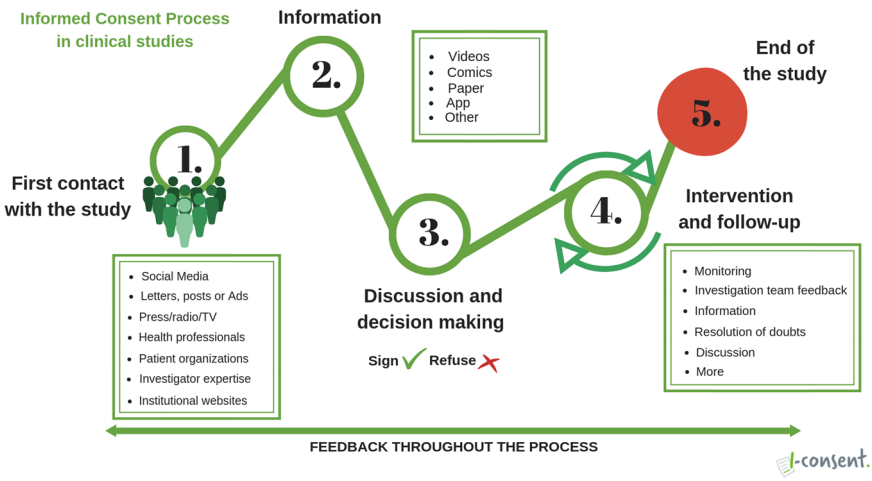


FIGURE 1 The informed consent process in clinical studies

To finalize the project, the guidelines were used to design patient information for the VIGIRA study (EudraCT No. 2019-001186-33, funded by Instituto de Salud Carlos III Research Grants) on the effects of an influenza vaccine in children aged 12–35 months during the 2019–2020 and 2020–2021 influenza seasons. The materials were designed WITH and FOR parents of children who could potentially participate in the study. In this case, cocreation was done through interviews with parents of potential participants. In addition, feedback from researchers and participants of the study in previous seasons was also used.

The i-CONSENT project has compiled and analysed legislation and ethical recommendations applicable in Europe, identifying the aspects that generate most uncertainty for the investigator, for example: how to adapt it to the needs of the potential participant, how to express it in plain language, how to assess its comprehension, how to apply gender and multicultural perspectives, and so forth. This analysis has made possible the elaboration of more specific recommendations on the informed consent process, which help to achieve the objectives set by the international bodies responsible for guaranteeing the protection and autonomy of patients participating in medical research.

The recommendations of the i-CONSENT project have been developed to complement and facilitate the implementation of international ethical guidelines and European and national legislation on clinical research.

ACKNOWLEDGEMENT

This research has been carried out in the framework of the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective (i-CONSENT)". The i-CONSENT project has been funded by Horizon 2020, SwafS-17-2016, Grant Agreement number 741856. This publication reflects the views only of the authors.

DATA AVAILABILITY STATEMENT

The article has no data.

Jaime Fons-Martinez MSc, Researcher Vaccine Research Area - FISABIO[1]
Cristina Ferrer-Albero PhD, Professor[2]
Javier Diez-Domingo PhDHead of Vaccine Research Area - FISABIO[1,2]

[1]*Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Valencia, Spain*
[2]*Facultad de Medicina y Ciencias de la Salud, Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain*

Correspondence
Jaime Fons-Martínez, Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Avda. de Catalunya, 21, 46020 Valencia, Spain.
Email: jaime.fons@fisabio.es

Jaime Fons-Martinez and Cristina Ferrer-Albero contributed equally to this study and are considered coprimary authors.

KEYWORDS

bioethics, clinical research, comprehension, informed consent, participant-centred design, research ethics

ORCID

Jaime Fons-Martinez http://orcid.org/0000-0002-8319-3658
Cristina Ferrer-Albero https://orcid.org/0000-0001-8904-0532
Javier Diez-Domingo https://orcid.org/0000-0003-1008-3922

REFERENCES

1. Tam NT, Huy NT, Thoa le TB, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. *Bull World Health Organ*. 2015;93(3):186-198H.
2. Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective [Internet]. CORDIS EU research results. European Commission. December 10, 2021. Accessed December 20, 2021. https://cordis.europa.eu/project/id/741856
3. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics*. 2013;14:28.
4. Chapman N, McWhirter R, Armstrong MK, et al. Self-directed multimedia process for delivering participant informed consent. *BMJ Open*. 2020;10(7):e036977.
5. Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies. *BMC Med Ethics*. 2021;22:138. doi:10.1186/s12910-021-00708-1

ANEXO 6: Co-creation of information materials within the assent process: from theory to practice

Received: 21 September 2021 | Revised: 29 August 2022 | Accepted: 10 November 2022

DOI: 10.1111/hex.13675

ORIGINAL ARTICLE

WILEY

Co-creation of information materials within the assent process: From theory to practice

Jaime Fons-Martinez MSc, Researcher[1] | Cristina Ferrer-Albero PhD, Vice-dean[2] | Javier Diez-Domingo PhD, Head of Unit[1,2]

[1]Vaccine Research Area, Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Valencia, Spain

[2]Facultad de Medicina y Ciencias de la Salud, Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain

Correspondence

Jaime Fons-Martinez, MSc, Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Valencia, Spain.
Email: jaime.fons@fisabio.es

Funding information

H2020 Science with and for Society, Grant/Award Number: 741856

Abstract

Introduction: The informed consent process is key to safeguarding the autonomy of the participant in medical research. For this process to be valid, the information presented to the potential participant should meet their needs and be understood by them. The i-CONSENT project has developed 'Guidelines for adapting the informed consent process in clinical trials' which aim to improve informed consent so that they are easier to understand and better adapted to the needs and preferences of the target population. The best way to tailor information to the characteristics and preferences of the target population is to involve the community itself.

Methods: Following guidelines developed by i-CONSENT, assent materials were co-created for a mock clinical trial of the human papillomavirus vaccine in adolescents. During the process, two design thinking sessions were conducted involving a total of 10 children and 5 parents. The objectives of the sessions were to find out the children's opinion of the informed consent (assent in their case) process in clinical trials, identify the parts that were most difficult to understand and alternatives for their presentation and wording, identify the preferred formats for receiving the information and the main characteristics of these formats, design a video explaining the clinical trial and evaluate a tool for assessing comprehension.

Results: Assent materials were co-created in three formats: a web-based material following a layered approach; a video in story format; a pdf document with an innovative way of presenting information compared to traditional assent documents. In addition, the Comprehension of Assent Questionnaire was co-designed, based on the Quality of Informed Consent questionnaire.

Conclusion: The design thinking methodology has proven to be an easy and useful tool for involving children in designing information tailored to their needs and preferences.

Patient or Public Contribution: A sample of the target population participated in the design and piloting of the materials created using design thinking methodology. In

Jaime Fons-Martinez and Cristina Ferrer-Albero contributed equally to this study and are considered co-primary authors.

addition, patient representatives participated in the design and evaluation of the guidelines developed by the i-CONSENT project that were followed for the development of the materials in this study.

KEYWORDS

assent, design thinking, ethics, information materials, informed consent process, participant-centred design

1 | INTRODUCTION

Many people still believe that the term informed consent (IC) is limited solely to obtaining the signature of research participants in the Informed Consent Form (ICF), unaware that this act is part of a much broader Informed Consent Process (ICP).[1]

During the ICP, efforts are made to protect the rights and welfare of participants at all times. The right to health protection is the main objective of legislators, researchers, sponsors, health professionals and the pharmaceutical industry. But the right to justice, freedom and participant autonomy must be ensured in all research involving human subjects.[2]

The ICP, described step-by-step in the 'Guidelines for tailoring the Informed Consent Process in Clinical Studies',[3] focuses on a continuous bidirectional communication process between the participant and the research team. It starts at the first contact of the potential participant with the study and continues until the end of the study and the corresponding dissemination of its results.[4]

There are therefore a series of phases in which relevant information is provided from the first contact with the potential participant. This information is discussed and clarified in an interview with a member of the research team who is trained to perform competently and with integrity.[1] The decision on whether or not to participate in the study should be made after ensuring that the potential participant has understood all relevant information provided and that any doubts that may have arisen have been resolved.

The central axis of the whole process is the relationship that is created between the researcher and the study participants. Knowledge, empathy, active listening, communication skills and respect should not be lacking in this relationship.

But since the interpersonal relationship that is created is not traceable and no record of what is discussed or talked about can be kept, it is necessary to ensure that the relevant information from any research study is presented and available to the potential participant in a clear, concise and patient-friendly manner.

The best way to adapt it to the characteristics and preferences of the target population is to involve the community itself, or a representative group of the community, in the design, development and execution of the ICP monitoring of the research, as well as in the dissemination of the results.[1]

In the same way that lay members are included in Ethics Committees to provide that perspective of potential participants, inviting lay members or patient groups to participate in the development of IC materials and resources will have a positive impact on the end result, as the process will be better understood and more suited to potential participants. Industry and patient organizations are committed to improving collaboration and building trust with all parties involved. The document developed by the European Federation of Pharmaceutical Industries and Association (EFPIA) on how to work with patient groups[5] is a reference point to guide these interactions.

This is the result of a shift from the traditional paternalist paradigm of care, inherited from Hippocratic medicine to a patient- and family-centred paradigm of care.

One of the first initiatives in this direction was the creation of Patient-Focused Medicine Development (PFMD) in 2015,[6] whose mission was to bring together and include all healthcare stakeholders in an open coalition for shared decision-making and to provide healthcare solutions. Among the outcomes of this collaboration, a practical guide was developed[7] for planning, developing and evaluating the quality of patient involvement activities and projects in the development and lifecycle of medicines.

Between 2012 and 2017, the European Patients' Academy on Therapeutic Innovation (EUPATI)[8] project was developed with the aim of increasing patients' involvement in the development and research of new medicines and treatments, improving their health literacy, becoming patient experts and empowering them in the management of their own health.

In the field of rare diseases, the Share4Rare project launched in 2018,[9] and seeks to empower patients by increasing their knowledge through information materials created in collaboration with patients.

With the aim of developing guidelines to help improve the ICP, the i-CONSENT project was launched in 2017.[4] One of the key points of the project is the inclusion of potential participants in the design and review of the information materials in a research setting, to ensure that they are understandable and tailored to the needs and preferences of the target population.[3]

Balik's[10] approach to providing patient- and/or family-centred care envisages three different approaches: 'doing to', 'doing for' and 'doing with'. When we apply this to the ICP, we are faced with the challenge of making IC materials with the patient, where potential participants are involved in all phases of the process, especially in the design of information materials. To do this, sponsors and researchers must first understand the target population and then incorporate them into the design, development and review of the information materials to make them more inclusive and tailored to the actual needs of the participants.[3]

Tool V proposed in the guidelines, entitled 'Methodologies and tools to incorporate the participants' perspective',[3] proposes design thinking and focus group methodology to identify problem areas in the IPC, define and prioritize these problems and develop joint ideas and prototypes to solve them.

The participant is thus an active part of scientific progress and not a passive research subject. Co-creation in the ICP within any study seeks to encourage fair and open participation and quality input based on the experience and expertise of all stakeholders.

This article describes the process of developing informational materials for a hypothetical clinical trial (CT) with children following the recommendations of the i-CONSENT project. It focuses on the description of strategies for the co-creation of materials based on the characteristics of the target population, their needs and preferences.

2 | METHODS

Taking for granted the social and scientific value that any research must have to be carried out, we worked on the design and co-creation phase of the information materials for a simulated study, following the recommendations of the i-CONSENT guidelines.[3] The steps to be followed in the development of materials are summarized in Table 1.

The scenario for the assent materials is that of the human papillomavirus (HPV) vaccine CT in adolescents, taking into account gender differences.

The target population and the scenario were defined according to the i-CONSENT project study protocol,[4] considering healthy children aged 12–13 years old for participation. In the same way and following the same protocol, the result of the co-creation work of information materials was validated in a later phase, measuring their comprehension in Romania, Spain and the United Kingdom. It was therefore necessary to create an information comprehension assessment tool.

The technique chosen to work with the target group was 'design thinking',[11–15] as it is a directly user-centred, action-oriented technique aimed at generating innovative solutions to a given problem. It involves several phases: empathizing, defining, devising, prototyping and validating or testing.

TABLE 1 Points to consider when preparing study information

☐ Have information materials been prepared taking into account the target population?
☐ Have you tested your communication materials with representatives of your target population? Have you tested it with men and women (if applicable)?
☐ Is the information clear and concise?
☐ Is the information relevant and complete?
☐ Has it been presented in a neutral/balanced way?
☐ Have you provided references to reliable sources of information?
☐ Does the study include placebo control? Have you informed participants about the details of its use and the placebo effect?
☐ Have you informed participants about incidental findings policy?
☐ Have you considered a range of media channels/platforms/formats?
☐ Have all the information materials been approved by an Independent Ethics Committee?

Source: *Guidelines for Tailoring the Informed Consent Process in Clinical Studies*.[3]

2.1 | Development of the design thinking sessions

Two face-to-face sessions were scheduled in Valencia, Spain. Recruitment was done through the paediatric network VIVA (Vaccine Institute of Valencia), together with members of the i-CONSENT team. Participants were boys and girls aged 12–13 years, with no previous experience of participating in CTs and in good health. This is a challenge for vaccine CTs, as participants have no experience with the disease and are not aware of the indirect benefit of their participation.

As the aim of the sessions was to prepare materials that could be useful and easy to understand for both those who have previously participated in CTs and have knowledge of the terminology and processes used in them, and those who have never participated in this type of research, it was decided to include only participants with no previous research experience, since they are the ones who, in principle, are at a disadvantage in understanding and have the greatest need for information. It was also considered that there may be a risk that those who had already participated in CTs could monopolize the conversation and make the rest of the participants uncomfortable because they were unfamiliar with certain terminology or processes. Convenience sampling was used, where three paediatricians from the VIVA network offered participation to parents and children in the consultation. Those who showed interest in participating voluntarily were invited to contact the i-CONSENT research team. All participants were informed of the purpose of the sessions, the benefit to other children, the inconvenience their participation might entail in terms of time and travel, the protection of their data and the right to withdraw at any time without giving any reason. They gave their assent to participate, and the parents gave their consent. A total of 10 children participated in the design sessions.

To create a safe and open space to increase comfort, trust and participation, the following strategy was applied:

(1) Sessions began with group dynamics focused on: introducing the participants and the researchers; informing them that other children had participated or were going to participate in similar sessions; highlighting the importance of each participant's role in the research, making them feel that a diversity of opinions among the participants was welcome and that all contributions were important to us.

(2) Many of the activities included written expression, with subsequent reading aloud by the researcher. This meant that an idea or answer was not attributed to any specific person, encouraged all opinions to be heard no matter who said it and prevented the exercise from being monopolized by any one participant.

2.2 | First session

The objectives of the first session were:

(1) Create a climate of trust and empathy between children, parents and the research team.
(2) Share views on CTs for vaccine development and identify wishes and needs relevant to the group of participants and their parents.
(3) Prototype assent materials with preferred formats.

Two members of the research team welcomed the five children and their five parents and acted as facilitators guiding the group through the process. The participants were introduced to each other using a dynamic presentation through a game with a ball to encourage interaction between them. With this playful component, a positive emotional climate was established and the relaxation of those involved was achieved.

As this was a group of healthy children with no previous experience of participating in CTs, and in order for them to understand what a CT is, a 5-min 11-s educational video in Spanish on how a CT is developed and conducted, produced by the European Communication on Research Awareness Needs (ECRAN),[16] was shown. The aim was to understand what would be really relevant for children and parents if they would participate in a CT with vaccines.

Subsequently, a role-play was conducted with a vaccine CT scenario, in which both children and parents participated by assuming a role (participant, parents, researcher or doctor) and following a given script. At the end of the role-play, participants were given a traditional assent form to read and make decisions. They were given the paper-based assent document, based on the ICF used in a real trial (EudraCT no. 2006-000764-85) and were given the time they needed to read it.

Participants expressed their emotions, using balloons on which they drew faces expressing their mood with the information received in the assent and how they would feel if they had to make the decision to participate in the CT at that moment. In this way, it was possible to better understand the problems experienced by the participants and the feelings they have in a situation such as this.

With the information obtained the focus of action could be defined by focusing on the aspects relevant to the participants. The format 'The (user) wants/needs (want/need) because (insight)' was used.

The information collected was clustered into different areas of improvement: information (purpose, risks, benefits, personal data, right to revoke, conditions, procedure), format (web, app, video, comic, text, oral explanation) and decision-making (individual, shared).

Once the focal points for action had been collected and synthesized, the question arose as to how we could devise and design the best solutions to the problems raised.

To this end, through brainstorming, participants reflected on the information presentation formats they would prefer and were asked to design a prototype of assent material (video and infographic).

With all this work (summarized in Table 2), the first session ended and their participation was thanked.

2.3 | Second session

The second design thinking session included more detailed tasks involving another five children at the same age. The objectives were different, as the results of the previous session were already being used as a starting point:

(1) Detect words that are difficult to understand, and propose a glossary of terms.
(2) Read the modified written assent document for the hypothetical HPV vaccine study to identify information that is difficult to understand and propose a plain language explanation.
(3) Evaluate the comprehension assessment tool.
(4) Assess the understanding of the information provided.

The second session began with a review of the previous session in the form of a narrative story, telling them about when and where the previous session took place, the characteristics of the children who participated, the objectives of the session and the results

TABLE 2 Objectives and methodology for the first design thinking session with children and their parents

Objectives	Methodology
Empathize	Presentation dynamic: 'passing the ball'
Identify and define	Viewing video on Clinical Trials
	Vaccine clinical trial role play and decision making with a traditional text-based reporting document
	Clustering to define areas for improvement: information and formatting
Devising	Brainstorming for alternative presentation formats
Designing prototypes	Design of prototypes with different formats (video and infographics)

obtained. The points for improvement identified in session 1 were presented on a whiteboard using a mind map. This allowed to focus the children's attention, introduce them to the topic and the progress of the first session and explain the objectives of the second session.

The mind map graphically represented the main ideas, highlighting the most relevant points and making it easier for the children to focus their attention and follow the story. The first area of improvement detected in the previous session referred to the amount of information included in the initial document. Following the guidelines set out in Fact Sheet IV of the i-CONSENT guide: 'Information to be given to potential participants during the information phase' and taking into account the EU 536/2014 Regulation on CTs,[17] the original information document worked on in the first session was adapted.

The title proposed as a result of the text adaptation was: 'Phase III study on the HPV vaccine in youth from 9 to 14 years of age'. The i-CONSENT guidelines recommend using inclusive language and avoiding gendered roles. We also followed the recommendations on the gender perspective included in the guidelines, which recommends developing a single material for all participants, in the event that there are no exclusion criteria based on gender; and the recommendations to adapt the information to the minor's age and maturity.

As the amount of information in the text document proved to be overwhelming in the first session, the information was presented using a layered approach, maintaining the completeness of the information provided. The first layer was prepared with the relevant information, and the second was left for further information and a glossary of terms difficult to understand.

To test the new assent document prepared for the second session, the participants were asked to mark in colour the words they did not understand. Members of the research team explained the terms they did not understand, and the participants were asked to write an explanation in their own words. The definitions were accompanied by their own illustrations, which provided guidance on the type of drawing and the aspects to be highlighted.

Thus, a glossary of terms difficult to understand was created with the participants to expand the information in plain language and use it in a second layer with additional information. It included the concepts of a placebo, vaccine safety, blood tests, confidentiality and the right of revocation.

In terms of format, as requested in the first session, the use of graphic components to complement the information such as icons, infographics and simple and easy-to-interpret images was added, making the written information more easily readable and understandable.[17]

The use of digital tools and/or multimedia components[18] and the possibility of offering the participants different formats to receive the information was worked on with the children. In both sessions, the four options most discussed were: text, video, comic and web. Through brainstorming, the children contributed their preferences and then worked on a prototype of a website to present the information.

It is important to consider the provision of information in written or digital format as a complement to, not a substitute for, face-to-face discussions with the research team. Evidence suggests that simple and brief consent forms, accompanied by a meaningful conversation between participants and researchers, can improve comprehension.[19]

To assess comprehension of the information, an Assent Comprehension Questionnaire for vaccine studies (abbreviated 'C-CAsIn' for 'Cuestionario de Comprensión del Asentimiento Informado') was developed in Spanish, based on the Quality of Informed Consent (QuIC).[20]

During this session, the comprehension of the items of the C-CAsIn questionnaire was analysed. Those items that raised doubts were rewritten with the children's help. The Likert-type response was adapted by changing the numbers (1–5) with small icons that graphically represented an emotion or idea (emoticons).

In the first part of the questionnaire, which assesses comprehension objectively, the response possibilities for each statement were represented by a green, smiling icon for 'agree' and a red, sad icon for 'disagree' (see Figure 1).

In the second part of the questionnaire, which assesses comprehension subjectively, the response possibilities were widened and broken down further, with the possibility of choosing between five degrees of comprehension between 'I understood NOTHING' and 'I understood EVERYTHING' (see Figure 2).

The last part of the questionnaire includes a series of general questions about previous experience in a CT, satisfaction with the information received, the preferred format for receiving the information and sense of understanding of all the information.

Before closing the session, a brainstorming session was held on how to improve the information received, how they would adapt it to an interactive format and what elements they would use to support the information (links, pop-ups, embedded videos, etc.). Table 3 summarizes the work done during the second session.

FIGURE 1 Possibilities of response for the objective part (Part A) of the C-CAsIn. C-CAsIn, Comprehension of Assent Questionnaire.

FIGURE 2 Possibilities of response for the subjective part (Part B) of the C-CAsIn. C-CAsIn, Comprehension of Assent Questionnaire.

Objectives	Methodology
Empathize	Narrative story and mind map explaining the previous session and placing the main issue in the centre (information in assent) and connecting the different strands or areas of improvement: information and format
Identify and define	Reread adapted information document design to identify poorly understood concepts and define glossary of terms for second layer of information
Designing prototypes	Web prototype design Brainstorming: features of narrated video
Validate/test	Test the assent comprehension assessment questionnaire Test the information received

TABLE 3 Objectives and methodology of the second design thinking session with children

TABLE 4 Comprehension of Assent Questionnaire (C-CAsIn) Part A

No.	Question	Agree	Disagree	Section of information
A1	I can decide to participate in this study without discussing it with my parents. Their opinion does not matter.			Decision-making
A2	One of the benefits of participating in this study is helping other children. What the researchers learn from me can be applied to others.			Indirect benefit
A3	The researchers have told me how long the study will take.			Procedures
A4	The study vaccine has been tested before in many girls and boys.			Procedures
A5	One of the objectives of this study is to see how safe the vaccine is.			Aim of the study
A6	One of the benefits of participating in this study could be improving my defenses against diseases.			Direct benefit
A7	After I decide to participate in this study, I will be randomly (like playing heads or tails) put in a group.			Randomization procedure
A8	I will know what group I am put in throughout the whole study.			Blinding Procedures
A9	If I receive the placebo, my defenses will improve.			Placebo Procedures
A10	Participating in this study does not involve any risk or inconvenience.			Risks
A11	By participating in the study, I would be helping the investigators to know more about the product they study.			Aim of the study
A12	The information that I have read explains who I have to talk to if I am worried or if I have any questions.			Further information
A13	If I do not want to participate, I can leave the study without any problem.			Voluntariness
A14	I have to stay in the study even if I want to quit.			Right to withdraw

3 | RESULTS

Ten healthy children with no previous experience in CTs and their parents participated in the design thinking sessions. All the children were 12–13 years old and lived in the Valencian Region.

The final design of the assent information materials for the hypothetical trial with minors was discussed with external design and digital communication experts.

The text was improved in terms of its linguistic readability using the Fernández-Huerta Index (IFH)[21] and the Flesch-Szigriszt Index (INFLESZ) readability scale,[22,23] using the web tool 'Legible'.[24] The full-text readability scores of the first layer were:

(1) IFH: 'easy' (80.46 points);
(2) INFLESZ index: 'fairly easy' (76.52 points);
(3) Estimated reading time: 6 min;
(4) Years of schooling needed to understand Crawford's[25] formula: 4 years.

Following the suggestions of the children, visual aids were added and the text was accompanied by images, animated gifs and photographs featuring children.

The sketches made by the children on the design of the website were taken into account for the visual and navigational design of the website. The website (Figure 3), offered the possibility of obtaining

TABLE 5 Comprehension of Assent Questionnaire (C-CAsIn) Part B

Num.	I understood…	I did not understand ANYTHING	I understood EVERYTHING
B1	That the study vaccine is being investigated.		
B2	That my participation in the study will help other children.		
B3	How long will I be in the study.		
B4	What the researchers are trying to achieve by doing this study.		
B5	What will be done at each visit.		
B6	The possible risks and inconveniences of participating in this study.		
B7	The possible benefits of participating in the study.		
B8	Which people will know that I am participating in the study.		
B9	Whom I will need to talk to if I have any questions or worries about the study.		
B10	That it is not compulsory for me to participate in this study.		

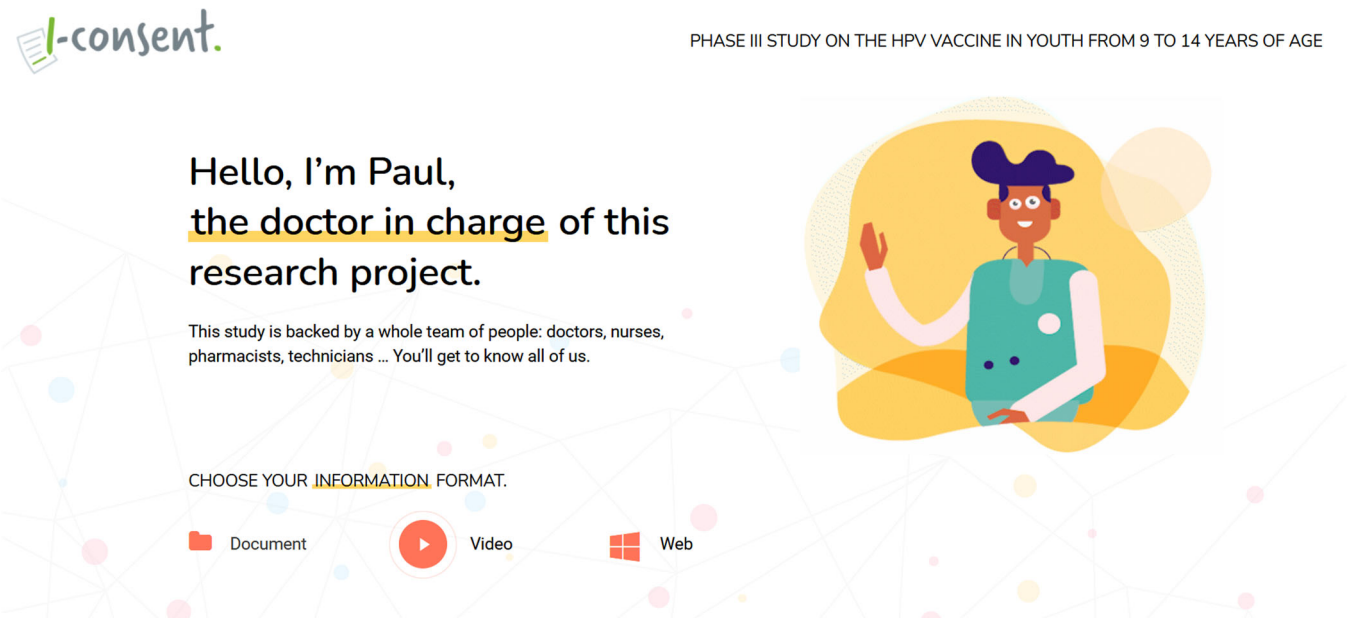


FIGURE 3 Screenshot of the final materials (http://iconsent.pilotvalidation.eu/en/teenagers-study/)

FIGURE 4 Sample of the information in 'document format' (http://iconsent.pilotvalidation.eu/wp-content/uploads/2020/04/Ingle%CC%81s-Adolescentes.pdf)

the information in the website, narrated video and/or written text (document in pdf format) with icons and images (Figure 4). At the bottom of the website, at the end of the information, the comprehension evaluation questionnaire was placed.

The final version of the *C-CAsIn* for vaccine studies was designed in collaboration with the children in several sections:

(1) Introduction: explanation of the study, objective, procedure, duration of participation, right to withdraw, voluntariness, decision making
(2) Part A—Objective (Table 4): 14 items written in plain language, with two response possibilities symbolized by facial expressions and colours, green for agreement and red for disagreement. The questions tested comprehension of all sections of the information provided.
(3) Part B—Subjective (Table 5): 10 items whose wording starts with 'I understood…'. The response possibilities are wider, with 5 possibilities between 'I didn't understand anything' and 'I understood everything'. Also symbolized by a colour code and a visual facial code.
(4) The last section of the C-CAsIn includes a short questionnaire with 8 items on sociodemographic data (age, sex and country of residence), previous experience of participation in a CT, the difficulty of the information received and preferred format and overall satisfaction with the information received.

The final digital assent form was created on a web page with a narrated video. All documents underwent several rounds of text adaptation, review of assent content requirements, review of the comprehension assessment tool, translation from Spanish into English and Romanian and linguistic adaptation for end users by native translators.

Finally, potential participants also tested the information prototypes, providing their final improvements which were taken into account before the information was uploaded to the target website and before validation in the target population of 620 children aged 12 and 13 in Spain, England and Romania.

Before final publication, it was checked that the recommendations for the preparation of the study information in the i-CONSENT guidelines had been followed (Table 1).

It should be noted that the sessions did not seek consensus, but took into account all ideas and positions expressed in the design of the materials. Priority was given to suggestions that were common to the majority of participants.

The final materials are available on the following websites:

(1) Spanish version: http://iconsent.pilotvalidation.eu/estudio-adolescentes/;
(2) English version: http://iconsent.pilotvalidation.eu/en/teenagers-study/;
(3) Romanian version: http://iconsent.pilotvalidation.eu/ro/studiu-pentru-adolescenti/.

4 | DISCUSSION

The process of designing the information materials for an ICP is perhaps the central part of any research study since it determines the potential participants' understanding of the information and, therefore, their autonomy in making free and informed decisions. This is also important to make the study population feel that they are at the centre of the research and that they participate and collaborate consciously and voluntarily.

There are various factors that influence the understanding and interpretation of the information a person receives, but it is the task of sponsors, industry and researchers to ensure that each and every participant understands it. The amount of information received by children before participating in a CT is overwhelming, as was seen in the two design thinking sessions conducted in this study. But, according to Regulation (EU)536/2014,[17] it should include the nature, objectives, benefits, implications, risks and inconvenience of the CT, rights and guarantees of their protection, right to withdraw at any time without any problem and without justification, the conditions of the study, including the duration of participation and treatment alternatives. Faced with this large amount of information, the proposal developed in this study is to use a layered approach to present it. The first layer would contain brief information on the aspects covered by the legislation, and the second and successive layers would allow for further information. In this way, the child who wishes to know more about a specific aspect can expand on this information.

All this information should be clear, concise and adapted to the child's capacity to understand, but little account is taken of the information that children really want and need to know, as Roth-Cline and Nelson[26] pointed out. The systematic review carried out by Fons-Martínez et al.[27] shows that information needs are not the same for legislators, children, their parents and members of the research team. Focusing attention on the needs of children, it is observed that their interest is especially directed towards procedures, confidentiality and benefits[28]; knowing why they have been chosen to participate and if other children like them have already participated to ask them about their experience.[29] In the study conducted by Tait et al.,[28] slight differences were found with respect to gender at ages 13–17, with girls showing more interest in obtaining more detailed information about the procedure, objective, benefits, voluntariness and right to withdraw, and boys more interest in the alternatives.

But the amount of information is one thing; the difficulty of reading and understanding it is another. The urgent need to improve the readability of the information a minor receives before giving consent was already highlighted by Grootens-Wiegers et al.,[30] following a systematic review where the gap between the readability of the information and the reading level of minors was observed. Documents are often long, their readability low[31] and the language complex, negatively impacting the ICP.[32] What may seem simple to read and understand for trial sponsors and researchers can be complex for participants. In the present study, the readability of the initial information was improved by constructing shorter sentences with simpler terms, fewer syllables and more direct grammatical structures.[33,34] In this process, the contributions made by the children were of great help, as they participated in the drafting of the aspects that were more difficult for them to understand after being explained by the researchers.

To facilitate reading, the text was accompanied by simple pictures which, although not proven to significantly improve comprehension of the information, do improve satisfaction and the child's subjective belief that their understanding is improved.[35]

Attempts to improve the formats of information materials presented to children participating in research have been numerous in recent years, but none of them conclusive. Although the improved readability of written text and the comic format were shown to improve the comprehension of some aspects of the information presented to children compared to a traditional text format,[36,37] children participating in our design thinking sessions preferred other more interactive formats. The video format and the combination with multimedia tools[18] have also shown improvements in understanding and satisfaction with the information received by children in numerous previous studies,[38–41] as preferred by the children who participated in the co-creation process of the present study.

It is possible that all of these novel proposals in previous studies would have shown a greater positive impact on children's understanding and acceptance if they had also been involved in the design process.[13] In this way, the information and format would have been better adapted to their needs and preferences. It is not about offering a wide variety, but about offering what each age group prefers. Even making information more readable and attractive to children does not ensure that they will understand it.

One of the fundamental problems is the lack of validated tools to assess the comprehension of information in minors participating in an assent process. Although it is best to assess the level of comprehension of information through a natural conversation between the potential participant and the researcher,[42] these tools make it possible to homogenize the process of verifying comprehension, provide an objective record of comprehension during the assent process and serve as a support for those researchers who are less skilled in carrying out this assessment through a natural conversation. Several studies have developed and validated tools, such as the MacArthur competence assessment tool for clinical research (MacCAT-CR)[43] to assess the competence of minors, and the QuIC,[20] which measures comprehension objectively and subjectively, in cancer patients involved in CTs. Other

studies such as Chaisson et al.'s,[44] Lee et al.'s[45] and Blake et al.'s[46] have developed ad-hoc questionnaires with true/false items, to measure comprehension improvement after an intervention; none of these tools have been validated.

Based on the QuIC, as it is the most widely used questionnaire in different studies to measure comprehension, we adapted and created a new version for children, with the children's participation. Their participation at this point was crucial, as all their contributions to the items and the presentation format resulted in a new questionnaire (C-CAsIn) that was shorter, more comprehensible and simpler in its response format.

Co-creating by involving children increases the complexity of the process of designing information materials, but the benefit for them is direct, as it is adapted to their needs, increases their understanding and autonomy and therefore improves the decision-making process.

The limitations found in the present study were related to the fact that the children were not real participants in the CT for which the materials were being developed, which could generate a bias in their response. Working with a sample of children living in the Valencian Region may affect the transferability of the results.

5 | CONCLUSION

This article describes the methodology for the design and elaboration of IC materials for CTs with children (assent) and defines the specific tools to be used.

To ensure that the informational materials are tailored to the child's maturity, preferences and needs, it is recommended that a representative group of the target population be included in the design of the materials.

The design thinking methodology has proven to be an easy and useful tool to involve children in the design of information adapted to their needs and preferences.

It is recommended to conduct two working sessions focusing on three main topics:

1. what information is relevant to them;
2. which concepts are difficult for them to understand and
3. in what format they prefer to receive this information.

This will improve their understanding and promote their autonomy.

In addition, as part of the assent process in a CT, it is necessary to confirm that the information provided to the child has been understood. The C-CAsIn survey has been designed, together with the children, to test understanding of information in the assent process of vaccine CTs, however, it should always be checked for its suitability to the particular study design.

ACKNOWLEDGEMENTS

We would like to thank Dafina Petrova Dobreva, Júlia García Bayarri, Sally Jackson and María Cubillo Díaz-Valdés for their contribution to the design of the design thinking sessions. Our thanks also go to the paediatricians of the VIVA network who facilitated the recruitment of participants for the study. Special thanks to the children who participated in the design thinking sessions and to their parents. Our thanks to the European Commission for funding the i-CONSENT project and to the partners who helped us to develop the guidelines followed in this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Jaime Fons-Martinez https://orcid.org/0000-0002-8319-3658

REFERENCES

1. Organización Panamericana de la Salud y Consejo de Organizaciones Internacionales de las Ciencias Médica. *Pautas éticas internacionales para la investigación relacionada con la salud con seres humanos*. Cuarta ed. Consejo de Organizaciones Internacionales de las Ciencias Médicas (CIOMS); 2016.
2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
3. i-CONSENT Consortium. *Guidelines for Tailoring the Informed Consent Process in Clinical Studies*. Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO). Generalitat Valenciana; 2021.
4. CORDIS EU Research Results. Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective (i-CONSENT). Grant agreement no. 741856. 2021. Accessed February 18, 2021. https://cordis.europa.eu/project/id/741856
5. EFPIA Patient Think Tank. Working together with patient groups. 2017. Accessed February 19, 2021. https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
6. Patient Focused Medicines Development (PFMD) [Website]. PFMD Governance. 2015. Accessed January 19, 2021. https://patientfocusedmedicine.org/wp-content/uploads/2022/01/Governance-update-April-2021.pdf
7. Patient Focused Medicines Development [Guidance]. Patient Engagement Quality Guidance (PEQG) version 2.0. 2018. Accessed January 22, 2021. https://patientfocusedmedicine.org/the-patient-engagement-quality-guidance/
8. CORDIS EU Research Results. European Patients' Academy on Therapeutic Innovation (EUPATI) Grant agreement no. 115334. 2017. Accessed November 08, 2020. https://cordis.europa.eu/project/id/115334
9. CORDIS EU Research Results. Social media platform dedicated to rare diseases, using collective intelligence for the generation of awareness and advanced knowledge on this large group of diseases (Share4Rare). Grant agreement no. 780262. 2018. Accessed March 19, 2021. https://cordis.europa.eu/project/id/780262
10. Balik B. Patient-and family-centredness: growing a sustainable culture. *Healthc Q*. 2012;15 Spec No:10-12.
11. Altman M, Huang TTK, Breland JY. Design thinking in health care. *Prev Chronic Dis*. 2018;15:180128.

12. Roberts JP, Fisher TR, Trowbridge MJ, Bent C. A design thinking framework for healthcare management and innovation. *Healthcare*. 2016;4(1):11-14.
13. Jackson SM, Daverio M, Perez SL, Gesualdo F, Tozzi AE. Improving informed consent for novel vaccine research in a pediatric hospital setting using a blended research-design approach. *Front Pediatr*. 2021;8:1-11.
14. Wolcott MD, McLaughlin JE, Hubbard DK, Rider TR, Umstead K. Twelve tips to stimulate creative problem-solving with design thinking. *Med Teach*. 2020;26:1-8.
15. Deitte LA, Omary RA. The power of design thinking in medical education. *Academic Radiol*. 2019;26(10):1417-1420.
16. Ensayos Clínicos. *ECRAN Project (ESP)*. European Communication on Research Awareness Needs (ECRAN); 2013.
17. Perrenoud B, Velonaki VS, Bodenmann P, Ramelet AS. The effectiveness of health literacy interventions on the informed consent process of health care users: a systematic review protocol. *JBI Database System Rev Implement Rep*. 2015;13(10):82-94.
18. Gesualdo F, Daverio M, Palazzani L, et al. Digital tools in the informed consent process: a systematic review. *BMC Med Ethics*. 2021;22(1):18.
19. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics*. 2013;14:28.
20. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent: a new measure of understanding among research subjects. *J Natl Cancer Inst*. 2001;93(2):139-147.
21. Fernández-Huerta J. Medidas sencillas de lecturabilidad. *Consigna*. 1959;214:29-32.
22. Barrio-Cantalejo IM. *Legibilidad y salud: los métodos de medición de la legibilidad y su aplicación al diseño de folletos educativos sobre salud*. Tesis doctoral. Universidad Autónoma de Madrid. Facultad de Medicina; 2007.
23. Barrio-Cantalejo IM, Simón-Lorda P, Melguizo M, Escalona I, Marijuán MI, Hernando P. Validación de la Escala INFLESZ para evaluar la legibilidad de los textos dirigidos a pacientes. *An Sist Sanit Navar*. 2008;31(2):101-208.
24. Muñoz Fernández A. *Legible: Analizador de legibilidad del texto*. 2018. https://legible.es/
25. Crawford A. *Spanish Language Fry-Type Readability Procedure: Elementary Level*. Vol 7. Bilingual Education Paper Series Evaluation, Dissemination and Assessment Center California State University; 1984:1-17.
26. Roth-Cline M, Nelson RM. Parental permission and child assent in research on children. *Yale J Biol Med*. 2013;86(3):291-301.
27. Fons-Martínez J, Calvo Rigual F, Díez-Domingo J, Nepi L, Persampieri L, Ferrer-Albero C. Contents of the minor's assent in medical research: differences between the scientific literature and the legal requirements. *J Biolaw*. 2019:37-52. doi:10.15168/2284-4503-399
28. Tait A, Geisser M, Ray L, Hutchinson R, Voepel-Lewis T. Disclosing study information to children and adolescents: is what they want, what their parents think they want? *Acad Pediatr*. 2018;18(4):370-375.
29. Unguru Y, Sill AM, Kamani N. The experiences of children enrolled in pediatric oncology research: implications for assent. *Pediatrics*. 2010;125(4):e876-e883.
30. Grootens-Wiegers P, de Vries MC, van den Broek JM. Research information for minors: suitable formats and readability. A systematic review. *J Paediatr Child Health*. 2015;51(5):505-511.
31. Ashkenazi I, Oster N, Feinberg P, Olsha O. Evaluation of length and complexity of written consent forms in English and Hebrew for participation in clinical trials authorized in one medical institution in Israel: a descriptive study. *Account Res*. 2020;27(3):138-145.
32. Taylor HE, Bramley DEP. An analysis of the readability of patient information and consent forms used in research studies in anaesthesia in Australia and New Zealand. *Anaesth Intensive Care*. 2012;40(6):995-998.
33. European Commission. *How to Write Clearly*. Publications Office of the European Union; 2011:1-16.
34. Plain Language.gov. *Improving Communication from the Federal Government to the Public*. Federal Plain Language Guidelines; 2011.
35. Adcock KG, Hogan SM, Elci OU, Mills KL. Do illustrations improve children's comprehension of assent documents? *J Pediatr Pharmacol Ther*. 2012;17(3):228-235.
36. Ferrer-Albero C, Díez-Domingo J. Does a comic style informed assent form improve comprehension for minors participating in clinical trials? *Clin Ethics*. 2021;16(1):37-45.
37. Grootens-Wiegers P, de Vries MC, van Beusekom MM, van Dijck L, van den Broek JM. Comic strips help children understand medical research. *Patient Educ Couns*. 2015;98(4):518-524.
38. Tam NT, Huy NT, Thoa LTB, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. *Bull World Health Organ*. 2015;93(3):186-198H.
39. Tait AR, Voepel-Lewis T, Levine R. Using digital multimedia to improve parents' and children's understanding of clinical trials. *Arch Dis Child*. 2015;100(6):589-593.
40. Tait AR, Voepel-Lewis T. Digital multimedia: a new approach for informed consent? *JAMA*. 2015;313(5):463-464.
41. Synnot A, Ryan R, Prictor M, Fetherstonhaugh D, Parker B. Audio-visual presentation of information for informed consent for participation in clinical trials. *Cochrane Database Syst Rev*. 2014;5:CD003717.
42. Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Assessment of the appropriateness of the i-CONSENT guidelines recommendations for improving understanding of the informed consent process in clinical studies. *BMC Med Ethics*. 2021;22(1):138. doi:1021203/rs3rs-366913/v1
43. Hein IM, Troost PW, Lindeboom R, et al. Accuracy of the MacArthur competence assessment tool for clinical research (MacCAT-CR) for measuring children's competence to consent to clinical research. *JAMA Pediatr*. 2014;168(12):1147-1153.
44. Chaisson LH, Kass NE, Chengeta B, Mathebula U, Samandari T. Repeated assessments of informed consent comprehension among HIV-infected participants of a three-year clinical trial in Botswana. *PLoS One*. 2011;6(10):e22696.
45. Lee S, Kapogiannis BG, Flynn PM, et al. Comprehension of a simplified assent form in a vaccine trial for adolescents. *J Med Ethics*. 2013;39(6):410-412.
46. Blake DR, Lemay CA, Maranda LS, Fortenberry JD, Kearney MH, Mazor KM. Development and evaluation of a web-based assent for adolescents considering an HIV vaccine trial. *AIDS Care*. 2015;27(8):1005-1013.

How to cite this article: Fons-Martinez J, Ferrer-Albero C, Diez-Domingo J. Co-creation of information materials within the assent process: from theory to practice. *Health Expect*. 2022;1-11. doi:10.1111/hex.13675

ANEXO 7: Guidelines for Tailoring the Informed Consent Process in Clinical Studies

GUIDELINES FOR **TAILORING THE INFORMED CONSENT PROCESS IN CLINICAL STUDIES**

Improving the guidelines for informed consent, including vulnerable populations under a gender perspective

I-consent.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Publishing entity: Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO). Generalitat Valenciana.

ISBN: 978-84-482-6547-2
Legal Deposit: V-827-2021
DOI: 10.5281/zenodo.4563938

AUTHORSHIP

Editors: Jaime Fons-Martínez and Javier Díez-Domingo

Authorship: i-CONSENT Consortium

- **FISABIO:** Javier Díez-Domingo; Jaime Fons-Martínez; Júlia García-Bayarri; Fernando Calvo Rigual; Dafina Petrova Dobreva; Mónica Vázquez Moreno; Valle Morales Cuenca
- **UCV:** Cristina Ferrer-Albero; Miguel Egea-Ferrer
- **UNESCO BIOCHAIR:** Alberto García Gómez; Serena Montefusco
- **LUMSA:** Laura Palazzani; Fabio Macioce; Margherita Daverio; Mirko Daniel Garasic; Leonardo Nepi; Loredana Persampieri
- **GSK:** Olga María Martínez-Casares; M. Reyes Boceta Muñoz; María Cubillo Diaz-Valdes; Francisco Javier Rubio Pomar; Elena López Santos
- **AND:** Dimitris Dimitriou; Andrew Rebera; Silvia Lorenzo Pérez
- **MRF:** Linda Glennie; Rosanna Russell; Elizabeth Rodgers
- **OPBG:** Alberto Tozzi; Sally Jackson

ACKNOWLEDGEMENTS:

The i-CONSENT Consortium wants to recognize the contribution of all the participants in the design thinking sessions, surveys, nominal groups and workshops done during the project, and also to the members of the ethical advisory board.

We would also like to thank all the experts who have evaluated previous versions of these guidelines and shared their feedback with us, including:

- The experts who participated in the workshop held in Brussels, February 2019 [a]: Begonya Nafria; David Greenberg; Dimitar Georgiev; Elena María Gobartt Vázquez; Ellen Ons; Jane Elizabeth Plumb; Mónica López Cuesta; Oana Falup Pecurariu; Stefano Semplici; Tirso Ventura; Tristan Fuller.
- The experts who participated in the assessment of the appropriateness of some recommendations included in the guidelines. November-December 2020 [b]: Bahri Priya; Carol Ewers; Herman Nys; JJM Van Delden; Julia Wade; Kari Sand; Katie Gillies; Laudi Gerber; Lembit Rägo; Lotte Klim; Natacha Vaz Liti; Patricia Pérez; Sabrina Grigolo; Stavros Terzakis.

[a] https://i-consentproject.eu/workshop-a-step-closer-to-improving-informed-consent/

[b] https://i-consentproject.eu/project-recommendations-undergo-a-final-round-of-revision-with-experts/

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TABLE OF **CONTENTS**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

GENERAL **INFORMATION**

These guidelines have been designed to provide information and evidence to assist with the development, or review of the consent process for use in clinical studies with human participants. These guidelines do not deal with issues related to informed consent in clinical practice.

The guidelines were developed by the i-CONSENT consortium. i-CONSENT (H2020, Grant Agreement number 741856) is a European Union H2020 funded program that aims to improve the information that individuals receive when deciding whether or not to take part in clinical studies. The guidelines were developed based on a review of the scientific and ethical literature; policy documents and legal instruments, enlarging the perspective also on international normative documents; comparative analysis of the legislations of selected countries; declarations of international organisms/ institutions; reports and guidance documents; stakeholder consultation. The deliverables and articles produced during the project, which have been used for the elaboration of these guidelines, are available in CORDIS on the project's website and a list is provided at the end of this document (section 4).

The multi-stakeholder i-CONSENT Consortium includes representatives from academia: Ateneo Pontificio Regina Apostolorum (UNESCOBIOCHAIR) and Libera Università Maria SS. Assunta di Roma (LUMSA); an investigation and public health center: Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO); the pharmaceutical industry: Glaxosmithkline S.A. (GSK); a small and medium enterprise: AND Consulting Group; a patient association: Meningitis Research Foundation (MRF); and a tertiary care academic hospital: Ospedale Pediatrico Bambino Gesù (OPBG).

Introduction

The consent process is an essential procedure that ensures the fundamental rights and freedoms of the participant, allowing them to voluntarily decide whether or not to take part in a study, with the option to withdraw at any time, without consequences.

The format of the consent process for clinical studies has remained relatively unchanged for decades. In its current format, typically a long and complex text document, there are still areas for improvement in order to promote clear communication between participants and investigators. Effective communication is essential to uphold the fundamental ethical principle of respect for the participant's autonomy.

Several guidelines, legal documents and legal instruments about the consent process have already been implemented. These cover what informed consent is and should be; why it is important in clinical studies; the main procedures to follow during the informed consent process and the minimum content to be covered. The i-CONSENT guidelines have been written in accordance with these documents and they should be read in conjunction with them.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

What do i-CONSENT guidelines add?

These guidelines provide ethical recommendations and practical tools that aim to make the consent process more comprehensive, tailored and inclusive.

They include a new and broader concept of the informed consent process, more focused on the participants, and incorporating their point of view in every step, starting from the design.

These guidelines represent a change in mentality that gives greater prominence to informed consent, turning it into a process that provides added value and prevents it from becoming a bureaucratic act focused solely on the participant's signature on the informed consent form.

These guidelines provide a step-by-step description of the informed consent process, and a checklist to implement comprehensive and inclusive informed consent, as well as 14 fact sheets and 6 tools with recommendations and examples to put ethical considerations into practice.

Scope and purpose

Who are these guidelines for?

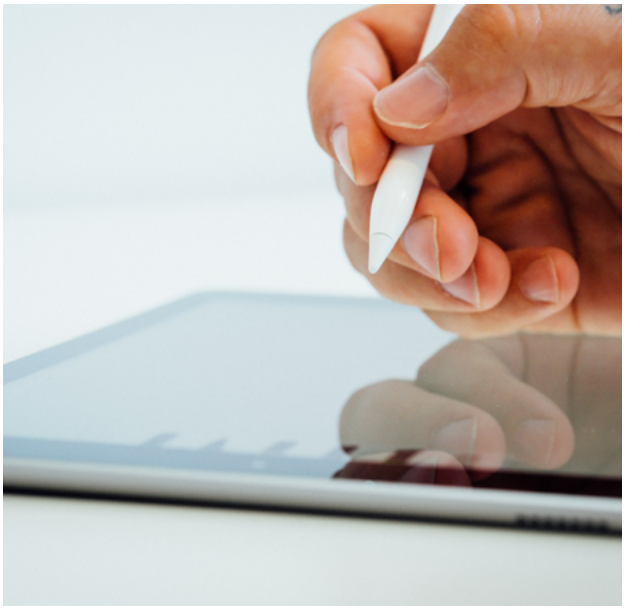
These guidelines are relevant for all stakeholders involved in the design and implementation of the consent process. They can support the work of investigators and sponsors, but are also relevant for ethics committees involved in the evaluation and approval of consent materials.

What is the purpose of the guidelines?

Their purpose is to enhance the consent process in clinical studies, to make it more understandable, and where possible, tailored to the participants' needs, preferences and circumstances to ensure that individuals can make autonomous decisions about their participation in clinical research.

How to use these guidelines

The guidelines are divided into four parts. The first part describes the i-CONSENT perspective on the consent process and highlights the need to improve the traditional approach to obtaining informed consent. This includes specific recommendations in order to tailor the informed consent process to the target population. Parts two and three provide practical TOOLs and recommendations to implement a tailored and more understandable consent process. Part four lists the scientific deliverables and publications produced as part of the i-CONSENT project.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

The contents of the four parts are:

1. CONSENT AS A PROCESS (Pp. 10-24)

This part of the guidelines explains four key aspects of designing a consent process that meets participants' needs: (a) clear and concise information; (b) interdisciplinary mixed-methods (quantitative and qualitative research methodologies) to gain informed consent design insights; (c) co-design as a central concept; (d) the importance of providing inclusive information and of personalizing the consent process to the needs of individuals. In addition to providing recommendations for each of these aspects, this part aims to change the way consent is conceptualized.

This part also describes the consent process step-by-step. It highlights the importance of understanding the process as a whole, rather than only focusing on the participants' signature on the form. It also provides specific recommendations for the informed consent (a) to apply a gender perspective; (b) when the studies involve minors; fertile, pregnant or breast-feeding women; participants coming from different cultural and religious backgrounds; or/and low-income populations.

2. CHECKLIST: STEP BY STEP GUIDE FOR INVESTIGATORS DESIGNING A CONSENT PROCESS (Pp. 25-28)

This checklist is a practical tool that aims to help investigators and organizations in fulfilling the requirements of regulatory, funding and other bodies. It also helps with identifying and reviewing all the key aspects that should be covered in the consent process.

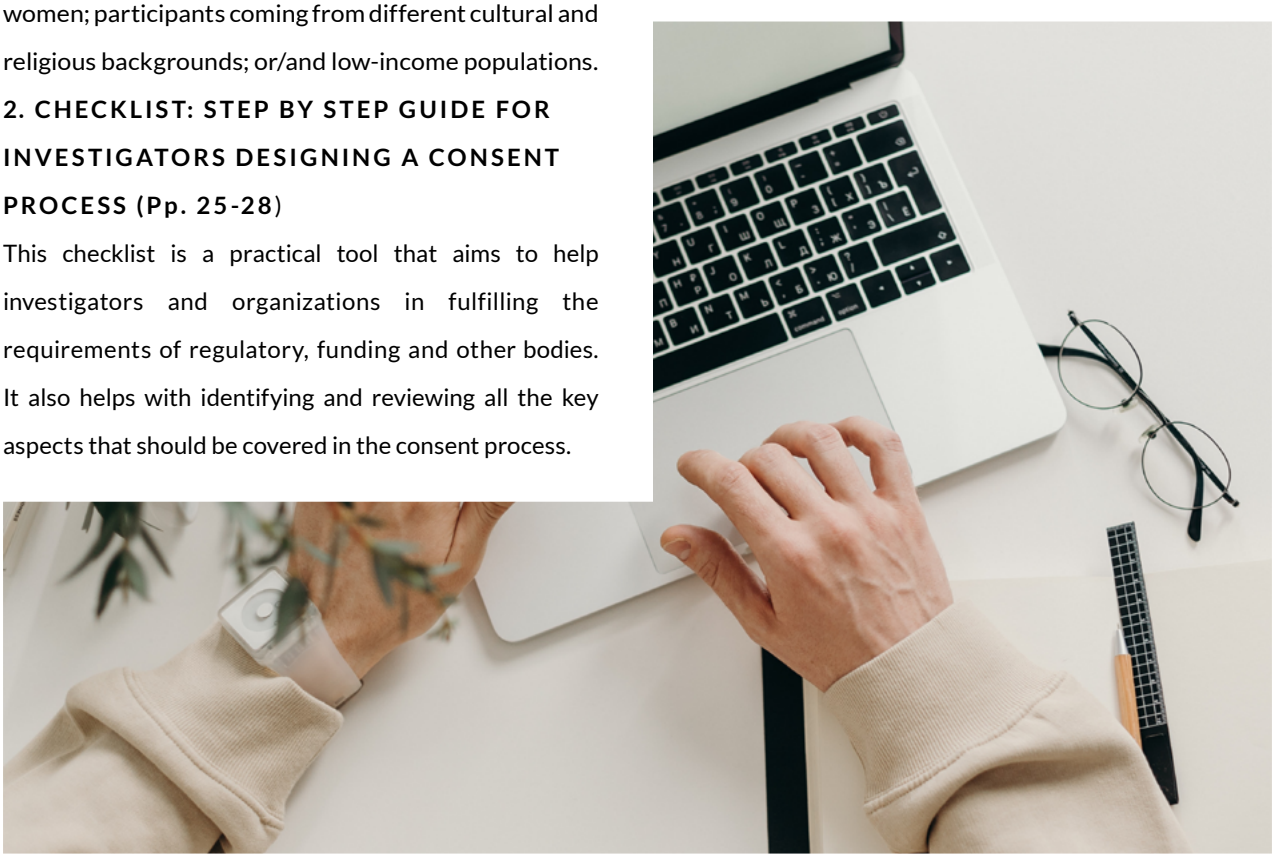
3. FACT SHEETS AND TOOLS (Pp. 29-58)

The third part of the guidelines provides a series of easy-to-read fact sheets and tools which complement the core document, highlight the importance of several aspects of the informed consent process, and provide recommendations on how to implement best practice. The fact sheets and tools also emphasize the different factors involved in the informed consent process. The fact sheets deal with aspects directly related to the informed consent process, while the tools include aspects that do not strictly belong to the informed consent process but are useful for its improved development.

4. LIST OF i-CONSENT'S SCIENTIFIC DELIVERABLES & PUBLICATIONS (Pp. 59-61)

This section contains a list of public deliverables and publications prepared in the framework of the i-CONSENT project, with links to each publication.

These publications have been used to produce the guidelines.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

The core elements of the i-CONSENT acronym

The acronym i-CONSENT contains the core elements of a comprehensive consent process (Table 1):

Table 1. The i-CONSENT acronym and core elements of the consent process

I	**Information**	Complete and clear information is essential for the potential participant to be able to make an autonomous decision.
C	**Co-creation**	The inclusion of potential participants during the design and review of study information materials is key to ensuring that they are understandable and address the target population's needs and preferences.
O	**Ongoing process**	Consent should be a two-way continuous communication process that begins at first contact with the potential participant, and continues until the end of the study.
N	**New technologies, methods, and (innovative) processes**	The consent process should include technical and methodological innovations to facilitate the participant's experience. Their appropriateness from a social, methodological, legal and ethical point of view should always be taken into consideration.
S	**Self-determination (autonomy)**	Autonomy is a fundamental principle. The purpose of the informed consent is to ensure that the potential participant is able to make an autonomous and free decision.
E	**Empowerment**	Participants should be empowered to make their own decisions.
N	**Nonstandard (inclusive and tailored)**	Research should be inclusive to meet the needs of the potential participants and respect the basic bioethics principle of justice. There is no single best way to conduct the consent process. The 'ideal' solution will differ in every setting and therefore needs careful design. Where possible, the consent process should be tailored to the needs of the target population.
T	**Trusted**	Good practices are essential to build trust between investigators and potential participants, and to increase society's trust in research.

Source: Own elaboration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

1. CONSENT AS A PROCESS

In recent decades, informed consent has become a long and complex paper document which provides information about the study and documents, via the participants' signature, their acceptance to take part in the study. In practice, it is regularly perceived primarily as a "bureaucratic" and legal requirement. Often, it is prepared by only one interested stakeholder without taking into account other points of view and frequently using technical language. This can result in a "legal" document rather than a process to inform the potential participant and to ensure their autonomy.

The i-CONSENT consortium acknowledges that the current process of informed consent may not ensure participants' understanding and, may therefore, hinder their autonomy.

The i-CONSENT consortium recommends that the informed consent process should be a continuous, bidirectional communication process that begins at the first contact with the potential participant and continues until the end of the study. It should incorporate key interventions designed to improve autonomy and inclusivity. This has the potential to generate research that is of higher quality, lower cost, and ethically justified.

It is crucial that informed consent enables a person to:

- Make an informed and autonomous decision about their participation in a study.
- Re-evaluate their participation throughout the study and understand their freedom to withdraw at any time.

The potential impact of better information and communication is high for clinical research, especially at an ethical level (safeguarding people's autonomy).

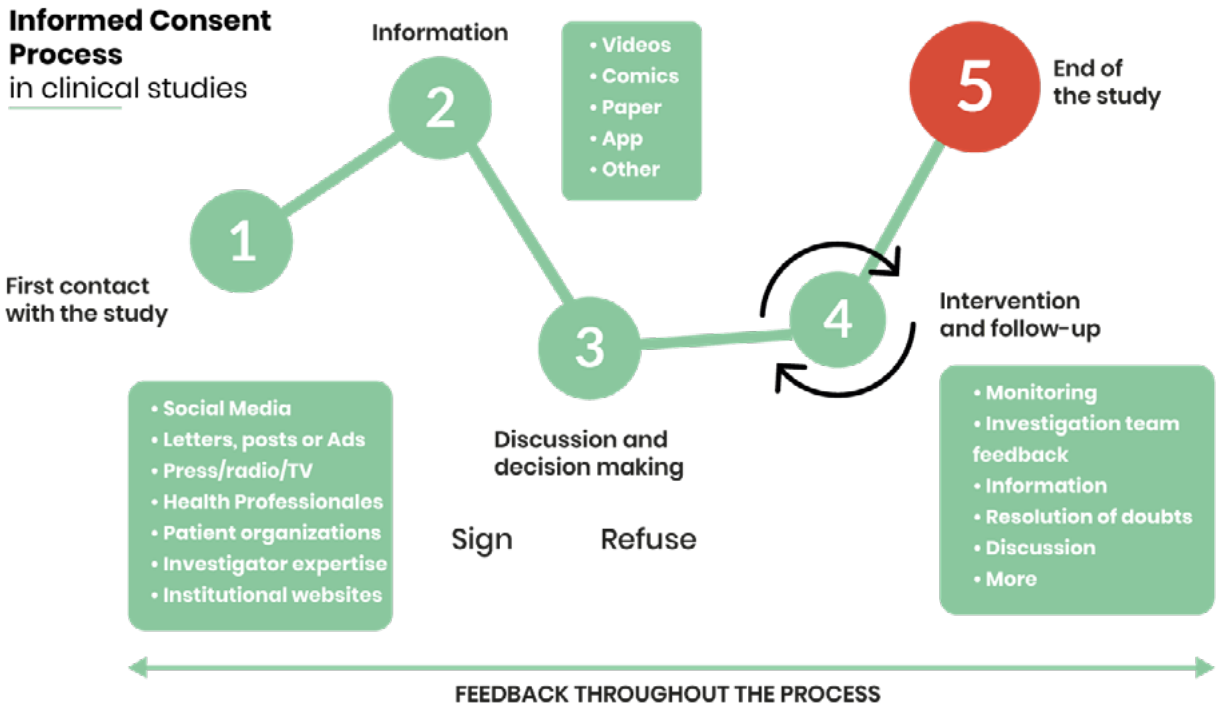
1.1 THE INFORMED CONSENT AS A PROCESS

i-CONSENT proposes a consent process for clinical studies that is designed to meet participants' needs. This process entails five different phases (Figure 1).

During the consent process, continuous feedback and communication between the potential or current participant and the research team is essential. Most phases can be done either face-to-face or virtually, depending on what is considered most appropriate for the study and target population. The consent process is also an opportunity to improve the health literacy of participants (FACT SHEET I).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Figure 1. The five steps of the Informed Consent Process in clinical studies



1- The potential participant's first contact with the study

The "First Contact" stage aims to raise awareness of the study and provide essential study information before the recruitment process begins. i-CONSENT recommends:

1. Considering different channels for recruitment.

The first contact can be established through different channels, such as health professionals, patient networks, institutional websites or social media; always taking into consideration the appropriateness from a social, methodological, legal and ethical point of view. It is vitally important that research is inclusive to ensure that health care interventions are fit for everyone. To abide by the principle of justice, and following the Declaration of Helsinki and the Clinical Trials Regulation, underrepresented groups should have opportunities to participate in studies, and this should be taken into account when designing the recruitment strategy. In clinical trials with drugs, it is important to ensure that the study sample is reasonably representative of the potential users of the drug.

Access to different communication channels varies across different groups in society, so recruitment channels need to be carefully selected.

2. Using transparent, balanced and neutral recruitment messages.

These messages should include objective information in neutral language. They should be clear and precise.

The information provided during this first contact should allow the potential participants to know if they are interested in the study and if they can participate (eligibility criteria).

3. Reviewing the recruitment strategy to ensure it is ethical.

The relevant independent Ethics Committees should review and approve all the materials and methods for recruitment, including advertising.

RELATED FACT SHEETS:

FACT SHEET II. PRESENTING STUDY INFORMATION

FACT SHEET III. ADVERTISING THE STUDY

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

2- Provision of information

After the initial expression of interest, potential participants should be provided with additional information about the research. This may be provided in formats tailored to potential participants' characteristics or preferences. The provision of excessive information ('information overload') can amount to misinformation and thus hinder the quality of the informed consent process.

i-CONSENT recommends:

1. Provide the participant with all relevant information about the study before the discussion with the investigator, ensuring that they have sufficient time to consider it and to prepare any questions that they may have.

This information should be delivered in a clear and concise way.

When providing information about alternative procedures or treatments, include information on effective treatments or tests available in other regions/countries. In some cases, particularly in translational research, participating in a clinical trial may be the only possibility of accessing a procedure or treatment (with uncertain results) because no other treatment/procedure is available or reimbursed in the region of the study. The investigator has the duty to inform the potential participants about the treatments/procedures available in other regions/countries as well.

2. Consider new technologies and formats to deliver information to complement face-to-face discussion.

Different instruments and media are used to deliver information to best meet the needs of the population. One way that technology could be used to convey relevant information is through audio-visuals. This format can be conducted remotely and, as it is delivered in the same way every time, the quality of delivery is consistent. Some factors that can enhance the impact of multimedia tools are to include interactive components or, in case of Randomised Clinical Trials, their use in presence of the investigator.

It is recommended to give more than one option of format (such as video, gamification or comic) that ensures that the information is delivered consistently and may improve the study understanding.

RELATED FACT SHEETS:

FACT SHEET II. PRESENTING STUDY INFORMATION

FACT SHEET IV. INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE

3. Discussion and Decision Making

3.1 - Discussion

After the information has been provided to the potential participant and they have had time to reflect on the content, the investigators should resolve the concerns about the study and the participation.

Face-to-face discussion between the potential participant and the investigator should ensure that the participant fully understands all relevant aspects related to their participation.

i-CONSENT recommends:

1. Selecting an appropriate environment for the discussion.

It should be conducive to facilitating the dialogue (e.g. a quiet, calm, and friendly environment) and it is essential to ensure privacy.

2. Strengthening the communication skills of the investigator.

The investigator providing information to the participant should have good communication skills. It matters not only

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

"what" is said but also "how" and "by whom". Investigators may speak to people of varying educational, cultural and social backgrounds and they should do so in an effective, caring and professional manner to convey a message and contribute to a participant's understanding of the study.

3. Checking potential participants' comprehension.

Comprehension is a key element of the Consent Process, and depends on the individual (maturity, educational level, etc.) and the investigator's ability and willingness to communicate. The investigator must ensure that potential participants have understood the relevant information about the study in order to make an informed and autonomous decision.

Related FACT SHEETs:

FACT SHEET V. INVESTIGATOR–PARTICIPANT RELATIONSHIP DURING THE CONSENT PROCESS

FACT SHEET VI. HOW TO ASSESS PARTICIPANT'S COMPREHENSION

TOOL 1. HOW TO BECOME A GOOD COMMUNICATOR

3.2 – Decision making

If the participant decides to take part in the study, a consent form should be signed and dated by both the participant and the investigator who conducted the discussion. A copy of the document should be provided to the participant.

In the case of minors, parental/legal representative consent is required, with the assent of the older minor, as well. When minors reach the legal age to consent during the research must have the opportunity to give their consent.

i-CONSENT recommends:

1. Ensuring that potential participants are able to make an autonomous decision about whether or not to take part.

The decision must be made without any kind of coercion, undue inducement or deception not only from the research team, but also from family members or other persons.

2. Using decision aids to facilitate the decision-making process.

A decision aid (for example animations, interactive information materials or infographics) is a useful tool designed to make specific and deliberative choices among various options and possible outcomes presented. It describes the decision to be taken, the options available, and the outcomes of these options (including benefits, harms, and uncertainties) based on a careful review of the evidence.

3.Providing support and give adequate time for participants to make a decision.

Participants should be given adequate time to consider their options, and they should be allowed to consult with others before making a final decision, if they wish to do so.

4. Ensuring participants are aware of all the information of the study and the possibility to withdraw at any stage.

It is important to highlight this information and ensure its understanding before the signature.

5. Obtaining feedback from participants.

Gathering experience and opinions of potential and current participants throughout the study can enable the informed consent process to be adapted to unforeseen situations and the different informational needs of participants. It helps to define and improve the process for both ongoing and future studies, making informed consent a dynamic process which can be adapted.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

RELATED FACT SHEETS:

FACT SHEET VI. HOW TO ASSESS PARTICIPANT'S COMPREHENSION

FACT SHEET VII. THE USE OF DECISION AID TOOLS

TOOL II. HOW TO GAIN PARTICIPANT'S FEEDBACK

4- Intervention and Follow up

Throughout the duration of the study, participants must have access to the information used during the recruitment process and be informed on how to access it.

If at any point in the study there are changes in the protocol or new, relevant knowledge becomes available, participants should be informed and they will have to re-consent. The new consent should be approved by the ethics committee.

In addition to these i-CONSENT recommends:

1. Ensuring that members of the research team are available to respond to questions or concerns participants may have throughout the study.

2. Providing updated study information to participants throughout the study.

It is recommended that research teams provide regularly updated information about the development and the status of the study, to give the participant an understanding of how the study is progressing overall. This information may be provided online to facilitate its access.

3. Obtaining continuous feedback from participants.

Feedback should be obtained at all stages, including during the intervention and follow up.

RELATED FACT SHEETS:

FACT SHEET V. INVESTIGATOR-PARTICIPANT RELATIONSHIP DURING THE CONSENT PROCESS

FACT SHEET VIII. WHEN IS RE-CONSENT NEEDED?

TOOL II. HOW TO GAIN PARTICIPANT FEEDBACK

5- Completion of the study

When the study ends, the participants must be notified and informed of the treatment assigned to them (if applicable) as well as the associated results, in accordance with the agreed incidental findings policy.

All information about the treatment assigned, the procedures carried out and the associated results should be registered in the participant's medical records. If the participant expresses that they do not want their results to be recorded, this must be taken into account.

In addition to these, i-CONSENT recommends:

1. Thanking participants for taking part.

A thank you letter (or another form of communication) expresses gratitude from the research team and the sponsor when the participant has finished their involvement. Thank you letters are a good opportunity to highlight the importance of participation in research and the objectives that each participant helped in reaching. It should include information about the study, and a summary of the available results.

2. Including participants in the first steps of result dissemination.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Participants may be included in different dissemination events addressed to them. A summary of results understandable to laypersons must be provided.

3. Asking participants for feedback on the process. Feedback should be obtained at all stages, including at the end of the study.

RELATED FACT SHEETS:

TOOL II. HOW TO GAIN PARTICIPANTS' FEEDBACK

TOOL III. GUIDANCE ON CREATING "THANK YOU" LETTERS

TOOL IV. CREATING A SUMMARY OF THE RESULTS FOR LAYPERSONS

1.2 DESIGNING CONSENT WITH STUDY PARTICIPANTS

When Barbara Balik, BS and MS in nursing and doctorate in educational leadership, talks about how to deliver patient- or family- centeredness healthcare, she explains that the process can be characterized in 3 different stages: the "doing to"; "doing for"; and "doing with" stages . This can be also applied to the informed consent, where we need to shift from an approach where the informed consent is done TO the potential participant to one in which the informed consent is done WITH the potential participant.

Informed consent has to move from the "doing to" perspective, where the sponsor or the investigators decide what information the potential participant should receive, to a "doing for" perspective were potential participants are asked about their experiences and are considered when designing the informed consent. We should finally arrive at a "doing with" perspective, where potential participants are involved in the design of the informed consent, making them central to the process.

i-CONSENT proposes a "doing with" perspective for the informed consent process in three steps (see Figure 2) where sponsors and investigators seek to understand their target population (Understand), and incorporate them in the design, development and review of the informed consent (Co-create), to ensure materials are more inclusive and tailored to potential participants' actual needs and preferences (Outcome).

Some key design points are relevant during all the consent process. General i-CONSENT recommendations are provided here:

Figure 2. How to improve consent materials by placing potential participants at the centre of the design process

1. Balik B. Patient-and Family- Centredness: Growing a Sustainable Culture. Healthcare Quarterly. 2012; Vol.15 Special Issue:10-12

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

UNDERSTAND

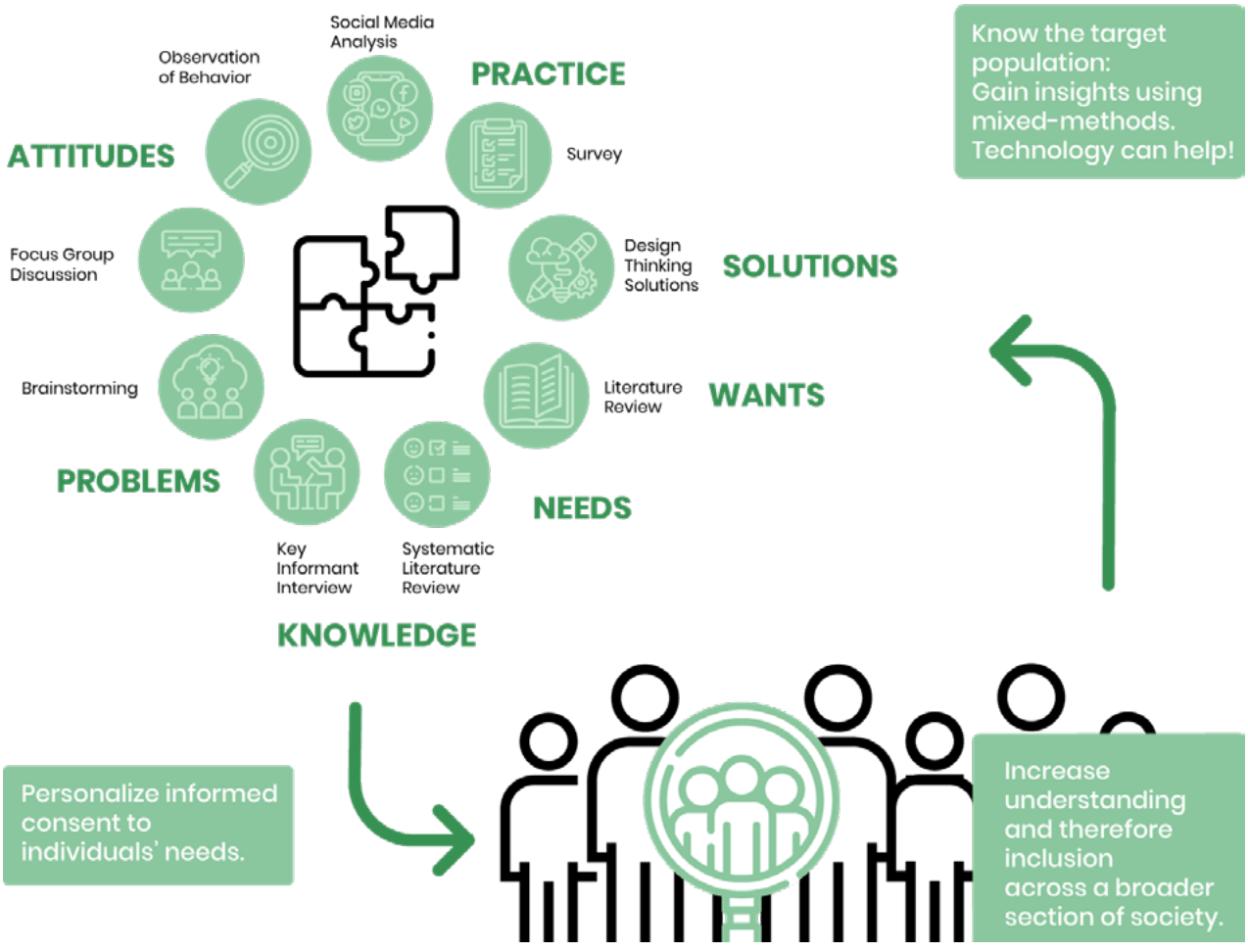
Use interdisciplinary quantitative and qualitative methodologies to learn about your study population, their interests and needs.

When obtaining consent, an understanding of the target study population is essential to ensure that information is provided in a way that is appropriate to their needs.

Insights on needs can be obtained using a variety of methods (Figure 3). It may be useful to explore the available literature on the target population (e.g. systematic or narrative literature review); ask the target population directly (e.g. interviews; surveys; design thinking); seek advice from experts (e.g. key informant interviews; brainstorming…); observe the target population; and/or analyse their interactions on social media and blogs.

Technology provides new opportunities to help gain insights from society (for example, analysing their interaction on social media and blogs or doing electronic surveys) and personalize informed consent to users (such as using a layered approach for presenting the information in a website), while new methods from other disciplines (for example, design thinking) help us turn insights into action.

Figure 3. Methods that can be used to better understand your target study population



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

CO-CREATE

It is important to consider the way in which the potential participants experience the consent process. They should play a central role, together with other stakeholders, in all design phases (Figure 3). While many qualitative and participatory research methodologies can be used to gain insights for the consent design process (TOOL 5), there is also a lot to learn from disciplines such as Human Centred Design.

The points of view and expertise of other stakeholders (such as investigators or ethical and legal experts) should also be taken into account when preparing informed consent materials.

It is highly recommended that consent materials are tested with representatives of your target population before their use.

RELATED FACT SHEETS:

TOOL V. METHODOLOGIES AND TOOLS TO INCORPORATE THE PARTICIPANTS' PERSPECTIVE

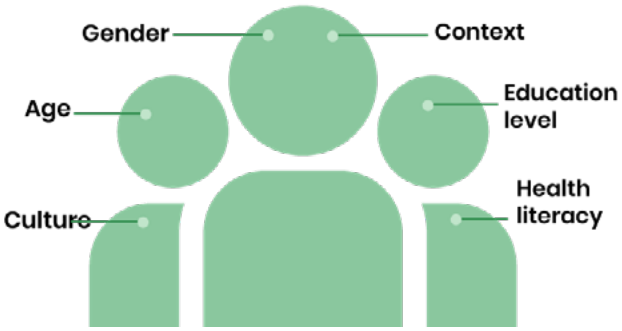
OUTCOME

Provide clear and concise information.

Ensure that the information is:

- Relevant: according to the nature of the study (objectives/ type of study/ phase…) and to your target population.
- Complete: to ensure that potential participants do not need to seek additional information from other sources.
- Easily understandable: use plain language, avoiding the use of jargon and acronyms. Throughout the consent process, all information provided to research participants should be tailored to their health literacy level.
- Neutral/balanced: Information should be presented using impartial and transparent language. It is important not to mislead the participant into having unrealistic expectations or therapeutic misconceptions.

Figure 4. Individual factors that may influence potential participants' needs during the consent process.



Provide inclusive information and consent tailored to individuals' circumstances.

To be inclusive, the information provided should meet the diverse needs of the potential participants, in their specific context. Potential participants' preferences for consent are unique and influenced by multiple factors, some of which are represented in Figure 4. Needs may also change throughout a person's lifetime, for example a woman's needs may change when pregnant or breastfeeding.

The discussion between the potential participant and investigator provides an ideal opportunity to address the participant's individual needs. Recommendations include using a layered approach for presenting information, and providing different channels and formats to receive information or communicate with the research team. Technology also provides new opportunities to tailor informed consent to participants (such as presenting the information in a website using a layered approach).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

1.3 TAILORING THE CONSENT PROCESS TO THE TARGET POPULATION

The Clinical Trial Regulation (REGULATION (EU) No 536/2014) establishes that, unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups that are likely to use the medicinal product investigated in the clinical trial, for example gender, age or ethnic groups. If a specific group is excluded from or underrepresented in the clinical trials, the protocol should include an explanation of the reasons and justification for these exclusion criteria. This representation criterion is also recommended for other clinical studies.

In this section we give recommendations for consent processes with a gender perspective; and for studies with specific populations (pregnant, breastfeeding or fertile women; minors; people from different cultural and religious backgrounds; low-income populations).

1.3.1 The gender perspective during the consent process for clinical studies

A lack of participation by women in clinical studies may produce a source of gender inequality. A gender perspective must be included during the consent process to ensure it is inclusive and to avoid stereotyping.

International Ethical Guidelines for Health-Related Research Involving Humans, Commentary (CIOMS, 2016) on Guideline 18 (Women as research participants) highlight that despite the current general presumption that favours the inclusion of women in research, in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, and the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on the information provided to them.

Differences between sex and gender and how they influence the informed consent

The informed consent process may be influenced by sex and gender differences.

- "Sex" refers to the biological condition and anatomic differences between males and females.
- "Gender" refers to the psychological, social and cultural dimensions that influence men and women's behaviours and roles.

Based on sex:

Female and males are biologically different, so:

- They may have different responses to medications.
- Fertile, pregnant and breastfeeding women require specific protection measures, as stated in the Clinical Trial Regulation (REGULATION (EU) No 536/2014). In these specific cases, information should be adapted to women physiological conditions (section 1.3.2).

Based on gender:

Gender differences are **socially constructed**; they **differ** from one society to another and they can be **changed**.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

The ones presented here come from different studies that indicate the existence of different behavioral trends between women and men (most of them included in i-CONSENT's deliverable 1.2). They only show general trends may vary, **they are not categorical.** To apply a gender perspective it is important to understand the five characteristics of the concept of gender (Table 2): relational; asymmetric/hierarchical; historical/changing; contextual specific; institutionally structured.

Table 2: Characteristics of the concept of gender

Relational	Gender refers to the relationship between women and men, not to them in isolation.
Asymmetric/hierarchical	These relationships often privilege one group. They usually give more value to the characteristics and activities associated with the masculine, contributing to produce unequal power relations.
Historical/Changing	It is based on historical traditions and practices that evolve and change over time and space. They are susceptible to changes by interventions.
Contextually specific	Gender's relationship and characteristics change depending on the multiple identities women and men have (age, ethnicity, sexual orientation, social and cultural stratum, etc.). They differ in all contexts due cultural traditions and practices.
Institutionally structured	It refers not only to relationships at the individual and private level, but also helps to perpetuate gender-related beliefs through infrastructure such as laws, religion, politics, etc.

Sources: Escuela Andaluza de Salud Pública [2] (2010) and World Health Organization[3] (2011)

Gender differences that may influence the consent process are of varied nature:

- Societal: as Cassese and Zuber[4] point out, women generally have less free time to participate in clinical studies, since they tend to take on "Double burden" (paid jobs and household chores) more than men.
- Preferences and use of Information and Communications Technology (ICT): men and women tend to evaluate and use technology differently: generally women use the internet more as a communication tool [5] while men as an information seeking tool[5] and overall women and men use different styles and strategies in online discussions[6,7]. There are also gender-based differences in eye tracking behaviour[8,9].

2. García Calvente, MdM (ed.). Guía para incorporar la perspectiva de género en la investigación en salud. Spain: Escuela Andaluza de Salud Pública; Observatorio de Salud de las Mujeres. 2010.
3. Gender mainstreaming for health managers: a practical approach. Faciltators' guide. Participant's notes. WHO 2011.
4. Cassese M, Zuber V. Clinical trials and gender medicine. Ann Ist Super Sanità. 2011; 47(1): 100-3.
5. Jackson LA, Ervin KS, Gardner PD, Schmitt N. Gender and the Internet: Women Communicating and Men Searching. Sex Roles. 2001;44(5/6):363-79.
6. Tsai MJ, Liang JC, Hou HT, Tsai CC. Males are not as active as females in online discussion: Gender differences in face-to-face and online discussion strategies. Australasian Journal of Educational Technology. 2015; 31(3).
7. Caspi A, Chajut E, Saporta K. Participation in class and in online discussions: Gender differences. Computers & Education. 2008;50:718-24.
8. Alt64, AIMC. Estudio Eyetrack Medios España: Análisis del comportamiento visual de los internautas y la efectividad de la publicidad online. España; 2005.
9. Mueller SC, Jackson CP, Skelton RW. Sex differences in a virtual water maze: An eye tracking and pupillometry study. Behav Brain Res. 2008;193(2):209-15.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

- Relationship and communication between investigator and participant (and vice versa): differences may be due to the gender of the investigator, the gender of the participant and how they interact in different contexts.
- Motivations and decision making procedures: scientific studies suggest that women tend to be more health conscious[10]; are more likely to thoroughly read the informed consent document, more information seeking, more cautious to avoid manipulation[11]; and are more likely to decline participation in clinical studies[12,13,14] .
- Disparities in experience and treatment: Hoffmann and Tarzian[15] indicate that "women who seek help are less likely than men to be taken seriously when they report pain and are less likely to have their pain adequately treated". Due to this gender-based bias.
- Male patients are consistently given more time and attention from medical professionals than female patients with the exact same symptoms.
- Communication:
  - There are more similarities than differences in the communication between men and women, and the differences are not categorical.
  - Male and female communication styles are often influenced by gender stereotypes[16].
  - Male and female communication styles are not attributable to men and women respectively. Men and women use characteristics of both communication styles and change from one to another depending on the circumstances. For example someone may take on characteristics usually attributed to the feminine style (more conciliatory) when talking with his/her boss or to a police officer who is rebuking him/her, and may take a more masculine style (more authoritarian) when speaking with his/her subordinate. In these cases, the position will have more influence on communication style than the sex of the speaker.
  - As well as gender, other factors influencing communication must be taken into account. They may include age, cultural and religious backgrounds, socioeconomic status or cultural patterns, among others.

Recommendations for a gendered approach

- Take into account the ways in which gender influences health needs and concerns, including the different roles and interests of women and men, as how health messages are received.
- Ensure materials are inclusive. Test and retest messages, concepts, and intended program formats with women and men to ensure that they work well for both. Adapt consent materials by gender only when the strategy or study is directed to a single sex group (for example, when only male participants or pregnant and/or breastfeeding women are recruited to a study).
- Use multiple communication strategies to ensure that services, supplies, and practices of the chosen media do not reinforce gender stereotypes.
- Adapt the informed consent process, especially during the interview, to the characteristics of the participant

10. Friesen LR, Williams KB. Attitudes and motivations regarding willingness to participate in dental clinical trials. Contemp Clin Trials Commun. 2016 Jan 12;2:85-90. doi: 10.1016/j.conctc.2015.12.011. eCollection 2016 Apr 15.
11. Knepp MM. Personality, sex of participant, and face-to-face interaction affect reading of informed consent forms. Psychol Rep. 2014;114(1):297-313.
12. Knepp MM. Personality, sex of participant, and face-to-face interaction affect reading of informed consent forms. Psychol Rep. 2014;114(1):297-313.
13. Petty DR, Zermansky AG, Raynor DK, Vail A, Lowe CJ, et al. "No thank you": why elderly patients declined to participate in a research study. Pharm World Sci. 2001 Feb;23(1):22-7.
14. Simons-Morton DG, Chan JC, Kimel AR, Linz PE, Stowe CL et al. Characteristics associated with informed consent for genetic studies in the ACCORD trial. Contemp Clin Trials. 2014 Jan;37(1):155-64.
15. Hoffmann DE, Tarzian AJ. The Girl Who Cried Pain: A Bias Against Women in the Treatment of Pain. J Law Med Ethics. 2001;29(1):13-27.
16. See Cameron D. Gender. In: Brown K, editor. Encyclopedia of Language & Linguistics (Second Edition). Oxford: Elsevier; 2006. 733-9 p.; Griffin E. A first look at communication theory. 8th ed. New York: McGraw-Hill; 2012.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

(considering gender). Good communication between the investigator and participant is key.

- Provide opportunities for participants to discuss the trial with friends and family members, but consider whether the family group or the larger community network may unduly influence the woman's decision on whether to participate.
- In the case of women coming from different cultural backgrounds, consider using a cultural mediator with a gendered approach in order to bridge communication gaps. Permission to participate from the woman's partner cannot replace the individual informed consent of the woman herself.
- If possible, foster the role of women as research actors (as investigators; representatives of patient associations; and members of ethics committees) who can also contribute towards a better understanding of the needs of women enrolling in clinical studies to enable their participation.

1.3.2. Adapting the informed consent process to fertility, pregnancy and breastfeeding

Women could be vulnerable in research during pregnancy and breastfeeding. These specific circumstances may require special protections, as stated in the Clinical Trial Regulation (REGULATION (EU) No 536/2014). Article 33 of the Regulation addresses the issue of clinical trials on pregnant and breastfeeding women.

It is important to note that pregnancy and breastfeeding do not affect a woman's capacity to decide on their participation in research studies after having received adequate information.

When recruiting fertile women into a clinical trial, the informed consent process should include:

- That the clinical trial may put the foetus at risk, so during the trial and for some time after it has ended (specify how long), the woman should avoid pregnancy.
- The need to verify the absence of pregnancy through pregnancy tests during the trial.
- Respect for the woman's choices and moral or religious convictions regarding how to avoid pregnancy during the clinical trial, including abstaining from sexual intercourse.
- Information about risks related to contraception.

When recruiting pregnant women:

- The informed consent should include a clear description of the risk for both, the mother and the foetus.
- A close follow-up of the pregnancy, foetus and child is essential and should be clearly communicated during the informed consent.

When dealing with breastfeeding women:

Remember to inform about:

- The risks concerning the health of both the woman and the newborn.
- The possible excretion of the experimental drug into human milk. This should be monitored and the duration of exposure should be adapted according to the level of risk. This should be clearly communicated during the consent process.

Partner involvement during pregnancy, breastfeeding or when the trial can affect fertility:

- The woman should involve her partner in the informed consent process. Permission from the woman's partner cannot replace the individual informed consent of the woman herself.
- Men participating in research which is potentially toxic for gametes or foetuses should receive clear and detailed information on the risks of their participation, and involve their fertile or pregnant partners in the consent process.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

1.3.3. The informed consent process in clinical studies involving minors

Ensuring the best interests of the child is of fundamental importance. Children should be involved in the decision-making process, according to their age and maturity.

Research involving minors requires special protection for them because minors may be vulnerable in relation to age, maturity and development. These reasons will affect their ability to understand, appraise and express their opinion, and that should be treated with special care.

Consent process in clinical studies with minors

- A clinical trial study with minors can only be conducted when informed consent by their legally designated representative has been obtained.
- It is important to ensure that children are involved in the decision-making process, according to their age and maturity.
- Minors should be informed about why the study involves minors; the nature and the purpose of the research; related risks and burdens (discomforts); and expected benefits (direct or indirect). They should also be given the opportunity to ask questions and express an opinion on whether or not they would like to participate (assent). Information must be given in accordance with the maturity of the child.
- A minor's wish not to participate should be considered binding if the minor is mature. Parental consent, without the minor's assent, is sufficient only if a direct benefit is expected to be obtained (for the best interests of the child), risks and burdens are minimal and the minor is not sufficiently mature to express a valid objection.
- A participant reaching the legal age to consent (according to national legislation) during the research will need to sign the consent for the first time for their participation.

NOTE:

Clinical Trial Regulation (REGULATION (EU) No 536/2014), Article 32, indicates the requirements and conditions that must be met in clinical trials with minors.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

How to adapt the information to the minor's age and maturity

Figure 5. How to adapt the information to the minor's age and maturity

1.3.4 The informed consent process in clinical studies involving people from different cultural and religious backgrounds

Cultural differences between investigators and potential participants in clinical trials can result in communication barriers, which are likely to hinder awareness about possible risks/benefits and therefore pose challenges to the informed consent process. In order to avoid this possible obstacle and to ensure that the process respects cultural practices, it is important to:

- Adopt procedures that incorporate an intercultural sensitive approach, which includes a deeper understanding and respect for people's cultural and religious backgrounds, to improve fairness and equity in research participation.
- Provide information in an easy-to-understand and culturally appropriate language.
- Promote the participation of trained cross-cultural professionals in the study.
- When appropriate, a translator and/or a cultural mediator should be available during the process of obtaining informed consent. They should be familiar with medical terminology and experienced in the relevant language, social habits, culture, traditions, religion and particular ethnic differences.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

- Deliver a translated informed consent form in a language and using terms understandable to the participant in order to provide trial related information adapted to the specific needs of families with a different cultural background. Particular attention should be focused on the appropriate use of local dialects and investigation-related terminology. Another challenge in presenting information to culturally diverse populations can be related to perceptions about the body, causes or prevention of diseases and different understanding of risks and benefits. Cultural differences could also impact upon a participants' perception of altruism, autonomy, risk aversion, etc.
- Use a participant-centred approach to communication which takes into account the needs and preferences of research participants. This also ensures respect for the cultural and religious values of the participant, fosters a good relationship between the participant and investigator, and builds long-term relationships between the community and the research team.

3 key steps to adapt consent process in different cultural contexts:

1. Be aware that key concepts can be understood differently.
2. Empathize/Sensibilize.
3. Where possible, adapt the consent process.

1.3.5 The informed consent process in clinical research involving low-income population

Special caution is needed when low-income populations are enrolled in clinical studies in order to ensure they have not been coerced (through social conditioning, pressures by medical staff or the research team) or unduly influenced to participate (financially, by offering better healthcare or by their family). It is important that these aspects are not underestimated due to other priority interests.

Investigators should ensure that potential participants with low literacy levels have fully understood all the benefits and risks relating to their enrolment in clinical research. Investigators should pay special attention to ensure that people from vulnerable social contexts have willingly consented to participate.

OTHER RELATED FACT SHEETS:

FACT SHEET II. PRESENTING STUDY INFORMATION

FACT SHEET IV. INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE

FACT SHEET V. INVESTIGATOR–PARTICIPANT RELATIONSHIP DURING THE CONSENT PROCESS

FACT SHEET VI. HOW TO ASSESS PARTICIPANT COMPREHENSION

FACT SHEET IX. THE INFORMED CONSENT PROCESS IN CLINICAL RESEARCH INVOLVING HEALTHY PARTICIPANTS

FACT SHEET X. INFORMED CONSENT AND THE USE AND STORAGE OF BIOLOGICAL SAMPLES AND DATA

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

2. CHECKLIST

A STEP-BY-STEP GUIDE FOR CONDUCTING THE CONSENT PROCESS

This step-by-step guide includes key points for good practice in clinical studies. Use of the guide can assist investigators and organisations to fulfil the requirements of regulatory, funding and other bodies and ensure that important issues have not been overlooked.

2.1 STEP 1: FIRST CONTACT WITH THE POTENTIAL PARTICIPANT

The first contact is the beginning of the recruitment process for potential study participants. This initial stage aims to provide essential information about the study, and explain the nature of participation and what it would involve, before the continuation of the full recruitment process. However, before an individual has the option to decide whether or not to participate, they must be aware that the study is being conducted. Investigators may therefore need to think beyond traditional recruitment techniques to ensure their target audience is reached.

Points to consider when designing a recruitment strategy:

- ☐ Have you identified your target group?
- ☐ Have you considered which methods you will use to identify the needs of potential participants?
- ☐ Have you considered what methods / professionals you will use for the first contact with potential participants?
- ☐ Have you included all the basic information in the first contact? (see FACT SHEET III)
- ☐ Have you ensured that information is presented in a neutral way?
- ☐ Has everyone who can participate had access to the information?
- ☐ Have you considered the use of different formats/ channels for the first contact? Have you considered the appropriateness of that media/format from a social, methodological, legal and ethical point of view?
- ☐ Have all your recruitment materials and methods been approved by an Independent Ethics Committee?

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

2.2 STEP 2: PROVISION OF INFORMATION

It is important to consider the provision of information in written or digital formats as complementary and not a substitute for face-to-face discussions between the potential participant and investigator. Evidence suggests that simple and shorter consent forms and increased dialogue between potential participants and study team members may improve understanding.

People typically show lower levels of comprehension when information is presented in long consent documents. In order to increase participant knowledge and understanding, use short and enhanced consent forms, translated into simplified documents (paper or electronic formats) with improved design. Consider text style, images/graphics, summary sections, booklets or leaflets, page layout, revised language, shorter sentences, improved readability, non-technical words, bullet points, different fonts, etc.

Points to consider when preparing study information:

- ☐ Have information materials been prepared taking into account the target population?
- ☐ Have you tested your communication materials with representatives of your target population? Have you tested it with men and women (if applicable)?
- ☐ Is the information clear and concise? (see FACT SHEET II)
- ☐ Is the information relevant and complete? (see FACT SHEET IV)
- ☐ Has it been presented in a neutral/balanced way?
- ☐ Have you provided references to reliable sources of information? (see FACT SHEET I and TOOL VI)
- ☐ Does the study include placebo control? Have you informed participants about the details of its use and the placebo effect? (see FACT SHEET XI)
- ☐ Have you informed participants about the incidental findings policy? (see FACT SHEET X)
- ☐ Have you considered a range of media channels/ platforms/formats?
- ☐ Have all the information materials been approved by an Independent Ethics Committee?

2.3 STEP 3: DISCUSSION AND DECISION MAKING

For a well-designed consent process, interaction between the potential participants involved in clinical studies and investigators is essential. The consent process should be adapted to meet the particular needs of individual study participants (see Section 1.3) and it should involve an ongoing, interactive conversation between the participant and the investigator, throughout the process. Establishing a relationship of trust, having good communication skills and cultural sensitivities (if applicable to the study) can improve the interaction between the research team and the participants.

A member of the research team must be available to explain the information and answer questions raised by potential participants.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

The discussion must clarify:

- all risks and benefits (direct or indirect) of participation
- what participation will involve (in terms of time commitments, procedures and the responsibility of participants).

Ensure that the potential participant has fully understood the information presented and the process, has adequate time to consider the information received and decide whether or not to participate, and has not been coerced.

Points to consider during the discussion and decision making process:

- ☐ Has the participant had appropriate time in a suitable environment to process the information?
- ☐ Have you checked that the participant understood all the information before signing the informed consent? (see FACT SHEET VI)
- ☐ Have you offered the potential participant a decision aid tool? (see FACT SHEET VII)
- ☐ Have you offered alternative communication channels between the participant and investigator to resolve any doubts about the study?
- ☐ Has informed consent been obtained before enrolling the participant in the study?
- ☐ Have you asked participants for feedback? (see TOOL II)

2.4 STEP 4: INTERVENTION AND FOLLOW UP

At this stage of the process, the research team should:

- be easily available to respond to any questions and concerns research participants may have;
- share any new and relevant information which becomes available;
- and provide study updates.

Points to consider during the intervention and follow up:

- ☐ Is the participant happy with their participation? If not, are they aware that they can withdraw at any time, without consequences?
- ☐ Have participants who become adults during the study consented to their continued participation?
- ☐ Have you ensured that participants know how to contact the research team?
- ☐ Have you checked if the latest version of the informed consent is being used? (see FACT SHEET VIII)
- ☐ Can the participant have access to the information used during the recruitment process?
- ☐ Have you asked participants for feedback? (see TOOL II)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

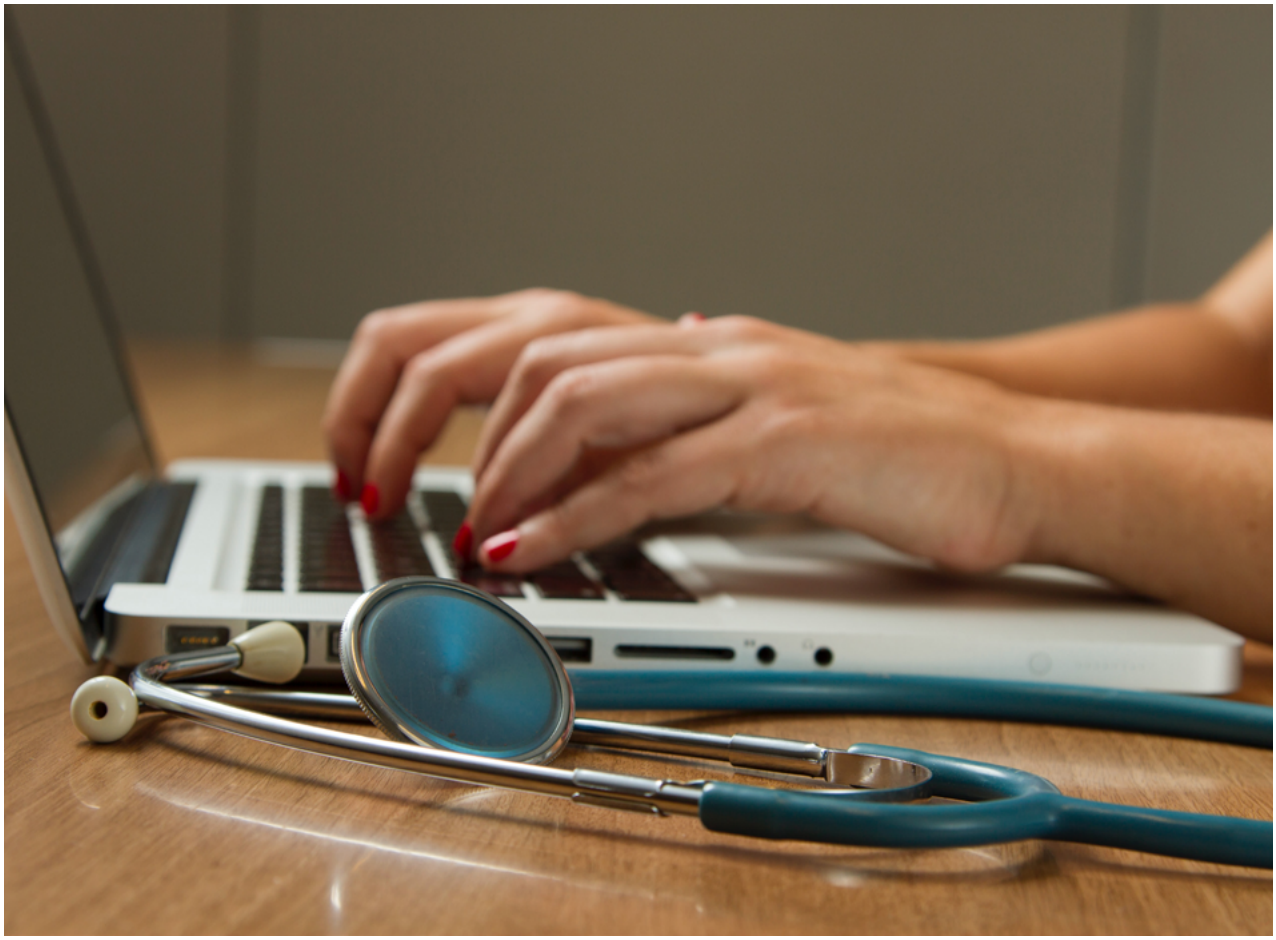
2.5 STEP 5: COMPLETION OF THE STUDY

Participants should be taken into account when disseminating the results and a lay-language summary of the finding should be accessible to them. The participants should be informed about when the summary is expected to be available and how they can access it (see TOOL IV) through a range of media.

The method of sharing information with participants, such as information about the treatment group assigned (in blinded clinical trials), must be planned in advance and offered to participants in a range of media channels/platforms/formats.

Points to consider once the study has been completed:

- ☐ Have you delivered the thank you letter to the participant? (see TOOL III)
- ☐ Have you asked participants for feedback? (see TOOL II)



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

3. FACT SHEETS AND TOOLS

The fact sheets deal with aspects directly related to the informed consent process, while the tools include aspects that do not strictly belong to the informed consent process but are useful for its better development.

3.1 FACT SHEETS

- FACT SHEET I. Communicating at the appropriate health literacy level for participants
- FACT SHEET II. Presenting study information
- FACT SHEET III. Advertising the study
- FACT SHEET IV. Information to give to potential participants during the information phase
- FACT SHEET V. Investigator-participant relationship during the consent process
- FACT SHEET VI. How to assess participant's comprehension
- FACT SHEET VII. The use of decision aid tools
- FACT SHEET VIII. When is re-consent needed?
- FACT SHEET IX. The informed consent process in clinical research involving healthy participants
- FACT SHEET X. Informed consent and the use and storage of biological samples and data
- FACT SHEET XI. Ethical considerations of using placebo control in clinical trials
- FACT SHEET XII. Informed consent, clinical research and covid-19
- FACT SHEET XIII. The use and storage of biological samples and data in clinical research in the covid-19 pandemic
- FACT SHEET XIV. Covid-19 clinical trials and patients' vulnerabilities

3.2 TOOLS

- TOOL I. How to become a good communicator
- TOOL II. How to gain participants' feedback
- TOOL III. Guidance on creating "thank you" letters
- TOOL IV. Creating a summary of the results for laypersons
- TOOL V. Methodologies and tools to incorporate the participants' perspective
- TOOL VI. Fake news and the reliability of sources

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET I.
COMMUNICATING AT THE APPROPRIATE HEALTH LITERACY LEVEL FOR PARTICIPANTS

Introduction

For many people in society, complex health concepts can be difficult to understand. Health literacy refers to the degree to which individuals have the capacity to comprehend, access and apply health information in order to make an appropriate health decision. Study information should be adapted to the health literacy level of the potential participant to enable them to make an appropriate decision about whether or not to take part. Participants' comprehension of the information provided through the informed consent process is one indicator of its quality. To enable comprehension, appropriate, accurate and relevant information should be provided in a language and format that is understood by participants. New technologies can be useful for communicating consent information. Investigators should ensure the accuracy of the information provided and the suitability of its communication.

Recommendations

Some practical tips for increasing health literacy include:

Use a glossary of terms to explain the more complex concepts. The use of dictionaries and links to "further information" is also recommended.

Ask open questions to assess understanding.

Provide information at a level of at least three years of education less than the average level of the target population. *See FACT SHEET II.*

Employ multimedia tools for a specific objective, always taking into consideration the characteristics of your target population.

Use storytelling formats when appropriate, e.g. with children.

Train your participants to improve their digital and health literacy. Critical thinking skills can empower citizens to freely decide which sources of information they prefer and what they share on social media.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET II.
PRESENTING STUDY INFORMATION

Use clear and concise information

Use a layered approach for presenting study information:

- In the first layer, provide a concise and non-technical summary of the study which provides the essential information that participants need to make an informed decision about whether or not to take part.
- In the second or further layers, include more detailed information.

Present information taking into account the interest of the potential participants, in an orderly manner. For example, a workshop with patient group representatives (i-CONSENT deliverable 1.6) revealed that ethical approval should be placed at the beginning of the document to reassure prospective participants that the research has been appropriately reviewed.

- Describe the purpose of the study early in the document.

Include the key points in booklets, leaflets or a flowchart to facilitate understanding.

Use graphics to complement information

Include graphics to facilitate processing and enhancing comprehension, independently of an individual's health literacy level. Graphics might include:

- Diagrams
- Pictures
- Icons
- Infographics

Provide information in different formats

Alongside with a personal and face-to face interaction, consider the use of digital tools or multimedia components, such as:

- Video with voice over
- Webpage with hyperlinks
- Mobile App

Give potential participants a choice of more than one format for receiving information.

Ensure written information is easily readable

Use plain language and avoid technical jargon:

- There are some guidelines or toolkits that can help. "The PRISM Readability toolkit"[17], for example, includes strategies, real-world examples and related resources to help investigators create easy to understand materials.

Measure the readability of a text by using validated indexes or tools designed for that language, such as:

- Dutch: Leesindex
- English: Flesch Kincaid Index and Reading ease score
- French: Kandel and Moles Modified Flesch Reading ease score
- German: Hohenheim Comprehensibility index
- Italian: GULPEASE index
- Spanish: Fernández Huerta index
- Swedish: Lasbarhets index

Jubelirer et al. indicate that "consent forms and other health education materials should be written at least three grade levels lower than the average educational level of the target population"[18] .

Ensure legibility: use appropriate font styles, sizes and colours; use images, tables and graphics properly.

- Some tools, such as the CDC's "Simply Put. A guide for creating easy-to-understand materials", provide guidance on this.

Include an easy to understand glossary of difficult to understand or technical terms

OTHER RELATED FACT SHEETS:

FACT SHEET IV. INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE

17. Ridpath JR, Greene SM, Wiese CJ; PRISM Readability TOOLkit. 3rd ed. Seattle: Group Health Research Institute; 2007.
18. Jubelirer SJ, Linton JC, Magnetti SM. Reading versus comprehension: Implications for patient education and consent in an outpatient oncology clinic. J Cancer Educ. 1994; 9(1):26-29.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET III.
ADVERTISING THE STUDY

The first contact with potential participants may be carried out in several ways, such as in person, by letter/email, telephone call, via an advertisement, etc. The method you plan to use must be appropriate from a social, methodological, legal and ethical point of view. All materials and methods selected for the first contact with potential participants must be approved in advance by an Independent Ethics Committee.

During the first contact:

- Provide information to potential participants in simple language.
- Avoid using content or language that could lead to misconceptions or promises of non-proven benefits.
- Ensure that any information about the study (such as explanations of the methods, scope of the study, etc.) is presented in an accessible way.
- Design the information to account for a possible lack of health literacy of the potential participant.

Considerations for different forms of communication

In person	Plan in advance what will be said to the potential participant to ensure that they are provided with all the necessary information. Rehearse the conversation beforehand.
Letter/email	Check if you are authorised to carry out the first contact. Decide in advance how you will manage non-respondents (if you will re-contact them, specify this in your first letter/email). Avoid including personal and confidential information as letters may be opened by someone other than the potential participant. Be cautious with the personal information included, as emails and letters can be unsecure channels.
Telephone	In order to protect the privacy of potential participants, this method is not recommended if there has not been previous contact with them. Plan what will be said to the potential participant and rehearse the conversation in advance.
Advertisement	Choose the most appropriate format (flyers, newsletters, websites, social media posts, posters, etc.) for your intended audience. Be aware of the language you use. Avoid inducement and use neutral language.

The information provided in the first contact with the potential participant should include:

- The purpose of the research, the importance of the study and expected duration.
- The target population with some inclusion and exclusion criteria (e.g. pregnant women between 18-40 years old).
- A brief description of the relevant study procedures (e.g. a routine blood sample).
- Contact person at the study site.

OTHER RELATED FACT SHEETS:

FACT SHEET II. PRESENTING STUDY INFORMATION

FACT SHEET IV. INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE PARTICIPANTS DURING THE INFORMATION PHASE

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET IV.
INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE

The European Clinical Trial Regulation (CTR) [REGULATION (EU) 536/2014] specifies the type of information potential participants must be provided with before they decide to enrol in a clinical research study, and this can be complemented by major international ethics guidelines[19].

The information elements to provide potential participants with can be arranged into four broad categories: (i) information about the research study; (ii) information about participants' rights; (iii) information about data protection; (iv) general information.

Information elements about the research study

- Aims and purpose
- Inclusion and exclusion criteria
- Methods and procedures, including planned genetic test
- Experimental aspects in the research and uncertainties related to the experimentation
- Approximate number of participants
- If other hospitals/research centres are involved
- Expected duration of participation
- Sponsors and funding sources
- Possible reasons for early termination
- Anticipated direct/indirect benefits
- Foreseeable risks or inconveniences
- Risk minimisation
- Alternative procedures of treatment
- Treatment options in case of harm
- Gratuity of participation
- Reimbursement for expenses related to study participation
- Limits of compensation in the event of injury or harm
- A copy of the ethics committee approval should also be made available to potential participants.
- Trial registration number (indication of when results available)
- Limits of compensation in the event of injury or harm
- A copy of the ethics committee approval should also be made available to potential participants.
- Trial registration number (indication of when results available)

19. WMA, Declaration of Helsinki - Ethical Principles for Medical Research Involving Humans, 1964, latest revision 2013, art. 26; CIOMS, International Ethical Guidelines for Health Research Involving Humans, 2016, Appendix 2 "Obtaining informed consent: essential information for prospective research participants"; ICH, Good Clinical Practice (E6), par. 4.8.10, provides a list of required contents for the informed consent form

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET IV.
INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS DURING THE INFORMATION PHASE

Information elements about participants' rights

- Right to receive information
- Right to ask additional questions or for clarification
- Right to receive any new information about the research
- Right to refuse participation

Information elements about protection of data

- Measures to protect confidentiality of medical health records
- Procedures for accessing personal medical health records
- Data collection, storage and/or the reuse of biological samples and further processing of previously collected personal data
- Consent for sharing or disclosure of data to third parties and for what purposes
- The storage of biological samples and possible further reuse of biological samples and personal data
- Conditions for disclosure of incidental findings

General information

- Identification of study as research
- Differentiation between research study and medical treatment
- Explanation of research methodology (e.g. randomisation, placebo, blinding etc.)
- Institutional affiliation of investigator(s)
- Contact details of investigator(s)

Sources:
WMA Declaration of Helsinki (2013), Regulation (EU) 536/2014, CIOMS International Ethical Guidelines for Health-related Research involving Humans (2016), ICH E6 (R2) Guidelines for Good Clinical Practice (GCP) (2016)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET V.
INVESTIGATOR–PARTICIPANT RELATIONSHIP DURING THE CONSENT PROCESS

Written documents, such as information sheets and/or booklets are an essential feature of the informed consent process, however the importance of the relationship between the participant and research team should not be overlooked. Effective investigator-participant relationships not only aid comprehension of complex medical information but can also help identify when a person's emotions, perceptions or expectations may interfere with their decision about participating in the study. Moreover, effective communication can result in a positive impact on study recruitment and retention and can help alleviate concerns a participant might have about clinical research.

Study comprehension	A positive relationship between investigator-participant is essential in ensuring that participants feel comfortable to ask questions, and can clarify their understanding, without feeling pressured to participate. Participants can sometimes feel overwhelmed after reading extensive and complex study information, but such effects can be reduced through clear and open communication.
Managing participants' expectations	Trustworthy and clear information is important to ensure that any person considering taking part in a trial is aware of what their participation will entail. Investigators are in a unique position to provide such information. Investigators should receive appropriate training to ensure that verbal communication is delivered in a balanced and complete manner. This communication contributes to create trust.
Children's assent and family dynamics	For clinical studies involving children, the importance of good communication and trust is even further emphasised. Research teams need to establish good relationships with both the child and parent. The ideal scenario would be the investigator, child and parents working as a team. Emphasis should be placed on all parties, including the child. All parties should share and discuss their concerns in order to agree on a decision that is in the best interests of the child.
Gender	Gender-based communication differences may affect the participant-investigator dynamic, both in the way investigators communicate and the way in which participants interact with the investigator. In research of a more sensitive nature (e.g. trials of vaccines against sexually transmitted diseases) it may be beneficial if the investigator in contact with the potential participant is of his/her same sex. However, the major focus should be on connecting with the individual participant, rather than making gender-based assumptions.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET VI.
HOW TO ASSESS PARTICIPANT'S COMPREHENSION

Comprehension is a key element of the informed consent process, directly determining its quality and how ethical principles are applied.

The best way to ensure that the potential participant has understood information about the study to make an informed decision, is through a conversation with the investigator. If the investigator does not have adequate communication skills, it is recommended that he/she seeks to improve them.

Additionally, there are some tools and methods that can be used to assess comprehension. Their use may, however, cause the potential participant to feel as if they are being evaluated or examined. As a result, these methods should not be the first choice to assess comprehension. Among these tools or methods we find:

Interview	The investigator should plan the interview in advance and include questions to assess participant understanding. The following method may help to assess potential participant's understanding: • Teach-back method: asking potential participants to describe in their own words their understanding of what they have been told by the investigator.
Questionnaires	The following proposed tools are validated questionnaires that can be used to assess a potential participant's understanding of the information: • Quality of Informed Consent (QuIC) [20] • Deacones Informed Consent comprehension test (DICCT) [21] • Brief Informed Consent Evaluation Protocol (BICEP) [22]

Source: own elaboration

Consider any therapeutic misconceptions or unrealistic optimism that participants may have when disclosing information, as this can prevent a person from understanding the risks and benefits and may prevent them from being able to properly evaluate the information they need.

NOTE: For investigators with good communication skills, natural conversation is the best option. Be careful not to give the impression of examining the potential participant.

OTHER FACT SHEETS RELATED:

FACT SHEET V. INVESTIGATOR-PARTICIPANT RELATIONSHIP DURING THE CONSENT PROCESS

20. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of Informed Consent: a New Measure of Understanding Among Research Subjects. JNCI. 2001;93(2):139-47.
21. Miller CK, O'Donnell DC, Searight HR, Barbarash RA. The Deaconess Informed Consent Comprehension Test: an assessment TOOL for clinical research subjects. Pharmacotherapy. 1996;16(5):872-8.
22. Sugarman J, Lavori PW, Boeger M, Cain C, Edsond R, Morrison V, Yeh SS. Evaluating the quality of informed consent. Clin Trials. 2005;2(1):34-41.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET VII.
THE USE OF DECISION AID TOOLS

What is a participant decision aid?

A tool that helps a potential participant make an informed decision. It describes the decision to be taken, the options available, and the outcomes of these options (including benefits, risks and uncertainties) based on a careful review of the evidence.

They are available in a variety of formats (i.e. online, paper based or video). Their purpose is to:

- Provide a structured method for potential participants to evaluate the available options.
- Encourage active engagement with the decision-making process.
- Help prospective participants reflect on their own values and preferences.

Ideally, potential participants should be given sufficient time to work through the decision aid. They should be given the opportunity to discuss the use of the tool with the clinician, before reaching their final decision.

Key benefits of using decision aid tools:

- To place the focus on the prospective participant. Although participants may expect the clinician to advise on the best option, ultimately, this decision must be made by the participant.
- To provide an accurate explanation of the risks.
- To present the information clearly and without bias.
- To allow the use of icons and other visual aids to help distinguish the pros and cons.
- To go beyond providing information, and seek to help people consider their own values.

Decision aids support prospective participants to:

- Improve their knowledge and understanding of the information given and their options.
- Make choices that are consistent with their values.
- Participate more actively in the decision making process.
- Have more accurate and realistic expectations of benefits and risks.

Pros
of the study

Cons
of the study

Further resources in: International Patient Decision Aids Standards (IPDAS); "Development and evaluation of decision aids for people considering taking part in a clinical trial: a conceptual framework" and "A systematic development process for patient decision aids"

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET VIII.
WHEN IS RE-CONSENT NEEDED?

Consent is ongoing but can be withdrawn at any time and dissent should always be respected. Under certain circumstances during the study, it may be necessary to re-affirm participants' willingness to remain in the study. This is referred to as "re-consent".

Circumstances that require participants to re-consent

- A substantive change in the conditions, procedures or protocol of the research.
- New information becomes available that could affect the willingness of participants to continue, for example, a new treatment alternative.
- In the clinical study, new elements appear regarding the use of data which were not stated in the original consent document.
- The original consent document has been improperly signed or documented.

Consent for the first time

It is the case of a participant initially unable to give consent, who reaches the capacity to consent.

- A minor participant reaching the legal age to consent (according to national legislation) during the research will need to sign the consent form.
- Alongside with consent for the first time, participants should be given the opportunity to give consent to the storage and use of his/her biological samples or data (if applicable).

Consent for a different use

The protocol for every study using stored human biological materials and related data must be submitted to the independent ethics committee, which must ensure that the proposed use of the materials falls within the scope specifically agreed to by the donor, if the donor has given broad informed consent for future research.

Re-consent is necessary:

- If the proposed use falls outside the authorized scope of research.
- If the initial consent does not cover purposes for future research.

New consent must be approved by an Independent Ethics Committee (IEC) or an Independent Ethics Committee (IEC).

Sources: elaborated from Resnik D (2009)[23]; Dixon-Woods M et al. (2017)[24]

23. Resnik D. Re-consenting human subjects: ethical, legal and practical issues. Journal of medical ethics. 2009;35(11):656-7.
24. Dixon-Woods M, Kocman D, Brewster L, Willars J, Laurie G, Tarrant C. A qualitative study of participants' views on re-consent in a longitudinal biobank. BMC medical ethics. 2017;18(1):22.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET IX.
THE INFORMED CONSENT PROCESS IN CLINICAL RESEARCH INVOLVING HEALTHY PARTICIPANTS

What is a healthy participant/volunteer?

The Royal College of Physicians[25] defines a healthy volunteer as *"an individual who is not known to suffer any significant illness relevant to the proposed study, who should be within the ordinary range of body measurements such as weight, and whose mental state is such that he is able to understand and give valid consent to the study"*.

Four points to be aware of:

1. Coercion and influence must not be used when obtaining informed consent.
2. Participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their inconvenience and time spent.
3. It should be clear that there is no financial compensation for the participation in a study. Ensure that participants are not influenced by economic reasons.
4. The participants' understanding of the risks should be carefully assessed. Investigators should be able to identify any healthy participants that are not fully aware of the risks of the study.

Key issues

Ensure that potential participant:

is not taking part in another clinical trial at the same time and is not motivated by reimbursement;

- understands the risks, the benefits and the absence of therapeutic benefits.
- understands all key features of the study, that participation is not compulsory and that they can withdraw at any time. To achieve this, the information should be adjusted to meet the needs of those with low literacy levels.

25. Royal College of Physicians. Research on healthy volunteers. A report of the Royal College of Physicians. J R Coll Physicians Lond. 1986;20(4):243-57.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET X.
INFORMED CONSENT AND THE USE AND STORAGE OF BIOLOGICAL SAMPLES AND DATA

Biological samples are often stored in biobanks in clinical research. Informed consent for the biobanking and re-use of biological samples and data has to be obtained in addition to consent for participation in clinical research. Remember that research participants and donors:

- must be previously informed about the collection, storage (time, place) and possible future uses of their biological samples;
- must be provided with a description of any planned genetic test;
- must be provided with the option of: consenting (or not) to research on biological samples for research directly related to the trial; and of consenting (or not) to the use of biological samples for research not directly related to the original trial;
- should be given the opportunity to withdraw from research, and to be assured of the removal and destruction of any stored samples and/or information;
- should be given the option for their biological samples to be 'anonymized' or 'pseudononymized' (or codified). With the first option the link between the biological samples and personal/clinical data of the participant is removed (this option, on the one hand undermines the meaning of research, while on the other guarantees privacy); the second option maintains the link between the samples and participant data, through a key under the investigator's custody (this option guarantees a measure of confidentiality, but this is not complete), but it is vital to building trust and enhancing involvement in research activities. "Pseudononymization" is in line with the European General Data Protection Regulation (EU) 2016/67. Participants should also be given an explanation of the advantages/disadvantages of each option;
- should be informed about data storage, risks of confidentiality and disclosure in certain circumstances.

Investigators should be transparent and inform participants and donors about the methods and goals set for the use of samples, drawing a clear distinction between research and therapeutic applications as a possible option. Participants who reach the legal age to consent during the research should be given the opportunity to give informed consent to the storage and use of their specimens or data.

The establishment of ethics committees in every biobank, who are in charge of supervising research and ethical conditions, carrying out surveillance on ethical standards and compliance with donors' consent is considered relevant.

ISSUES RELATING TO INCIDENTAL FINDINGS

An incidental findings policy between investigators and potential participants should be agreed through informed consent.

- Donors should be informed of expected or possible unexpected results, with regard to information relating to the diagnosis of ongoing diseases, the susceptibility/predictability of possible future diseases, also involving family members.
- Findings should be fed back when they are of immediate clinical relevance from a preventive, diagnostic and therapeutic level, and for reproductive choices. Adult participants should be given the opportunity to agree or decline this information and decide whether this information should be disclosed to family members. Investigators should ensure this even if the biobank has no diagnostic purpose.
- In the case of minors: parents should receive information relevant on a preventive, diagnostic and therapeutic level, and for reproductive choices. Communication about late-

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

onset disease should be discussed and included in the informed consent, also giving the option of the results being communicated only to the physician.

ISSUES RELATING TO CONFIDENTIALITY

Protection of personal data is required to guarantee the individual's right to confidentiality, through the anonymization, codification or pseudonymization of stored information that can be carried out on biological samples, tissues and/or collected health data stored for clinical practice purposes.

Data protection reduces the risk that information can be used for discriminatory purposes (i.e. in the field of insurance or employment), minimizing the possibility that stakeholders other than donors, family members, investigators and the scientific community might access personally identifiable information collected and stored for scientific purposes.

Confidentiality of health data is mandatory and should also be assured within the family in some circumstances, although information should not be shared with parents about minors if not necessary.

OTHER RELATED FACT SHEETS:

FACT SHEET IV. INFORMATION TO GIVE TO POTENTIAL PARTICIPANTS IN THE INFORMATION PHASE

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET XI.
THE USE OF PLACEBO IN CLINICAL TRIALS

Placebo is a very complex concept which means it should be clearly explained to the participants.

What information should be given to potential participants when the study includes the use of placebo control?

- Short description of placebo control and its use in clinical research
- Short description of possible placebo or nocebo effects
- Describe the procedures related to placebo control (possibility that not all the participants will receive the drug that is being tested, how many participants will receive placebo and how they will be selected, etc.)
- Describe any further possible risks
- The use of placebo in a research protocol is approved by the Independent Ethics Committee (IEC).

EXAMPLE OF INFORMATION TO DELIVER:

What is placebo?

Medline defines placebo as *"An inactive, non-drug compound that is designed to look just like the test drug. It is administered to control group subjects in double-blind clinical trials (in which neither the researchers nor the subjects know who is getting the drug and who is getting the placebo) as a means of assessing the benefits and liabilities of the test drug taken by experimental group subjects."* [26]

What is placebo effect?

An apparent result of a drug that occurs due to the patient's expectation of having received it, even though they have not. These effects can be positive (based on the expected effect of the drug) or negative (based on the expected side effects).

26. Glossary [Internet]. United States: The National Multiple Sclerosis Society. [cited 2021 February 23]. Available from: https://www.nationalmssociety.org/Glossary

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET XII.
INFORMED CONSENT, CLINICAL RESEARCH AND COVID-19

Clinical research is crucial in facing the health impact of the COVID-19 pandemic. However, even in the emergency setting due to the pandemic, scientific, ethical and legal requirements of biomedical research must be respected.

Despite the urgent need for quick advances in COVID-19 treatment, the ethical imperative to obtain informed consent remains. No matter how extreme the conditions, informed consent must be taken into account to ensure that those who decide to participate in the research can effectively understand risks and potential benefits, and make informed decisions.

Clinical trials during the COVID-19 pandemic

Even in the context of the pandemic emergency, the general ethical criteria of clinical trials should be respected, as should the relevant legal regulation:

- the scientific justification of the validity of the trials;
- the balancing of risks/benefits;
- the protection of health, safety and well-being of the patient/participant;
- the informed consent process;
- the informed consent process related to the use of biological samples;
- privacy and data protection requirements;
- the study review by independent ethics committees;
- the declaration of any conflict of interest from of all personnel involved in the study.

So called "regulatory flexibility" aims to guarantee the achievement of all these requirements, while accelerating as much as possible the process for scientific and ethical evaluation of clinical protocols concerning treatments for and vaccines against COVID-19. This has been instituted at international and national level, for example establishing scientific, regulatory and ethical bodies with the specific task of evaluating clinical studies related to COVID-19 at both a scientific and ethical level.

A trial of therapeutic treatments for COVID-19 must not exclude any subject, unless there is an unfavourable risk / benefit ratio. The exclusion of particularly vulnerable people from the trial is contrary to the principle of justice, as it deprives them of the same possibility of treatment, as no safe and effective treatment is currently available. Fundamental rights and freedoms, in particular the right to privacy, must be guaranteed.

The impact of the Coronavirus pandemic needs to be considered on both ongoing trials and new clinical trials. Participants should be informed regarding the impact the situation might have on the trial protocol, with possible changes in the risk/benefit balance and possible interruption of trials.

At every stage, it is very important for participants to be kept informed of changes to study and other plans that could impact their care. Since trial particivpants may not be able to visit the site for the protocol specific visits and investigations, sponsors should evaluate whether alternative measures such as virtual visits, alternative locations for assessment, including imaging centres and labs, could suffice, while ensuring the safety of the participant. This is important for trials that include participants who need additional safety monitoring.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Information regarding relevant therapeutic alternatives (if any)

Informed consent for clinical research also requires information to be provided about relevant alternatives that might be beneficial to the individual. It is the responsibility of the physician to properly inform the patient of any alternative clinical trial that would be a good option for patients. Clinicians may also be asked to make recommendations between multiple clinical trials, given the proliferation of COVID-19 studies.

Experimental protocols, vulnerability and the information process to the patient/participants

It is essential that researchers realistically balance the potential benefits and risks for research participants:

- avoiding trials in which the risks outweigh the possible benefits;
- evaluating risks and benefits considering the specific conditions of the patient, including situations of particular vulnerability;
- communicating risks and benefits in a clear and transparent way to potential participants;
- communicating scientific uncertainties related to the still scarce existing scientific knowledge about COVID-19.

Researchers have the responsibility to manage the information process and to carefully inform patients on the above mentioned aspects.

In particular, in trials for COVID-19 treatments, the best available standard of care should be guaranteed to all the patients participating in the trial. The identification of the standard of care, although difficult to determine, is a crucial ethical requirement for the study design and therefore for the information to the patient. In this specific context, randomized controlled trials are ethically controversial when offering participants randomization into a placebo arm that could produce serious harm including additional suffering, or even death. Adaptive and pragmatic clinical trial designs are the only methodological alternative, even if ethically challenging.

Researchers must consider the particular condition of vulnerability in the pandemic context and always evaluate the best interest of the patient, despite the possible request of patients to participate in a COVID-19 trial for therapeutic purposes.

Furthermore, researcher must consider informed consent in the context of the development of the disease (there are many decisions to be made at different times), choosing the appropriate time for the patient, considering their ability to understand and their emotional condition.

Despite the external pressure to start/conduct clinical trials, it is of paramount importance to respect the participant's decision-making process, considering – when there are uncertainties - that fear and discomfort can compromise confident and effective participation.

In addition, considering the existing general pressure for accelerating research in order to obtain useful results to combat the COVID-19 pandemic as soon as possible, researchers should carefully balance communication through social media of partial or in-progress scientific results. This is recommended in order to avoid the spread of so called fake-news that can result in disinformation or even in slowdown of research itself (for example because of the confusion generated by fake news amongst study participants).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Adaptive and pragmatic clinical trials

- Adaptive and pragmatic clinical trials search for a balance between the needs of clinicians to save lives and the needs of the medical and scientific community to obtain evidence of sufficient quality and scientific rigour.
- Pragmatic and adaptive trials designs produce true "experimental evidence", based on a methodology of pragmatism and adaptation: Pragmatism means that physicians continue to treat their patients without the restricted limitations of protocols, obtaining a rapid recruitment of a broad population without a precise standard of care defined at the beginning, which is likely to change during the trial; Adaptation means flexibility, considering possible change from the initial design as more data becomes available, considering the evolution of data.
- Adaptive and pragmatic designs can balance the rapidly changing standards of care with speed and agility.

Information process in the case of adaptive and pragmatic clinical trials

- Participants as patients should be correctly informed about the design of trials and how they differ from traditional trials, explaining the necessity of adaptation and pragmatism.
- Physicians/investigators should inform that participation in research encompasses uncertainties because of lack of knowledge about the best treatment: the absence of a standard of care should be mentioned explicitly in the informed consent and correctly explained to patients. This means that the patients should gain awareness that a pharmaceuticals considered beneficial at the beginning of the trials, could become harmful during the trial or at the end of the trial.
- It follows the obligation for the doctor to provide comprehensive, clear and comprehensible information with an empathic attitude.
- The shared purpose (of both physicians and patients) is to allow the patient to make an informed decision appropriate to the situation with proportionate and realistic expectations. Maximum transparency and clarity is required of the doctor especially if the possible side effects and potential harmful effects of the therapy are not known, so as to allow the patient to exercise their autonomy.
- This intense situation can produce an atmosphere of mutual pressure between patient and doctor: one expects a remedy at any cost and the other aspires to provide it in any way. The proportionality of the information should lie in the difficult relationship between the maximum expected benefit and the least foreseeable harm.

Informed consent and digital/other ways of consenting in a pandemic

Information provided by the researcher must also be transparent in the clarification of uncertainties: it is necessary to verify the participant's understanding, being aware that, in the context of the pandemic, the perception of risks has decreased, in face of expectations that are not always reasonable.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET XII.
INFORMED CONSENT, CLINICAL RESEARCH AND COVID-19

According to ethical and legal requirements for informed consent in an emergency situation:

- In compliance with health protocols in relation to SARS-CoV-2, exceptions to traditional written consent are allowed with the use of digital consent or oral consent in the presence of witnesses. In the latter case, it is important to confirm the patient's consent through third parties, that is, a person external to the health team and possibly to the health structure; also, where possible, the patient's consent should be confirmed with relatives on video call.
- When a patient is not able to receive and understand the information, but s/he is affected by pathological conditions without alternative treatment and it is not possible to promptly consult the trustee or a legal representative, for the authorization to prolong participation in a trial with potential direct benefits, consent should be obtained when it is reasonably possible to do.
- The doctor must comply as far as possible with the indications of any "advance treatment arrangements" or "shared care planning", and the indication of a trustee.
- In case of changes in protocols, which are frequent due to the evolution of the pandemic, consent must be, to the extent possible, requested again with the appropriate changes.
- Where it is not possible to obtain informed consent in the usual form (written consent), due to movement restrictions or patient isolation, alternative procedures should be considered, but as soon as the situation permits it, informed consent must be obtained.

Alternative procedures for obtaining consent can include:

- **oral or photographed/videotaped consent** in the presence of witnesses (selected according to impartial criteria justified by the investigator);
- **deferred consent**, according to ethical requirements (see the box below);
- **e-Consent,** using digital technologies for informed consent (avoiding paper and improving and speeding up information for patients), according to ethical requirements (see the box below).

Potential benefits of e-Consent

- It allows for enhanced infection prevention and control;
- Potential research participants can utilize Internet-connected device to virtually discuss the trial with researchers and access the informed consent document (advantage over paper consent forms, where the transmission of COVID-19 is possible);
- It facilitates a consent discussion with a patient who is not physically in the hospital. E-Consent also expands participations to populations traditionally not afforded clinical research opportunities through 'remote enrolment";
- Enhanced understanding, as e-consent often make use of boxed text and flexible text size, and incorporates multimedia tools that increase readability, engagement and retention. Ensuring critical information is available online enhances transparency and traceability, and verification of the regulatory process.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Off-label and compassionate use of drugs during the COVID-19 pandemic

In the context of the COVID-19 emergency, given the rapid spread of SARS-CoV-2, the severity of the clinical situation of some patients, the lack of resolutive care and the urgency of treatments for the protection of individual and social health, there is a strong push towards:

- **off-label** use of drugs: the use of a drug for clinical conditions that differ from those for which drug marketing has been authorized;
- **compassionate use** of drugs: the use of an experimental drug outside a clinical trial already in progress, for a single patient or for patients, for whom it is believed there may be a clinical benefit, on the basis of a defined clinical protocol or on a nominal basis for a single patient.

In both situations, patient(s) should be clearly informed about possible risks. Access to unvalidated therapies by compassionate use of drugs should never consist of a hidden experimental protocol, or a "shortcut" to accelerate the pace of research. Access to unproven therapies should not be a "hidden" trial, which, by means of compassionate use, obtains results by bypassing the usual lengthy trial procedures and authorization.

Furthermore, the public health threat posed by the pandemic does not justify coercive treatment.

Remember that:

- consent must be suitably informed, covering the uncertainties, the limits to hope and possible harmfulness or even lethalness;
- risk-taking should always be personal;
- off-label/compassionate use of drugs results should be always documented, to benefit from the results for the progress of clinical/scientific knowledge;
- a need to re-consent may be required in case of a newly approved therapy for COVID-19 (which would present an alternative to participation) or of new information on the therapy offered in the trial, discovered during treatment of prior subjects. With rapid changes in understanding of the disease, and hundreds of weekly publications focused on the topic, it may also be unclear how often such disclosure and re-consent should take place: this aspect should be carefully assessed.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Biological samples

Informed consent must always be required for the acquisition of biological samples, even in the case of serological tests and swabs.

- It should be specified whether they are taken for diagnostic and/or research purposes;
- As required in clinical research in general, consent must specify the time, place, storage methods of the samples and the purposes of the research, specifying whether it is directly related to research on COVID-19, as well as any subsequent use of samples for compatible purposes;
- In any case, the security of storage and the protection of privacy with pseudonymisation must be guaranteed in a manner that must be specified in the consent, to avoid any abuse and to be able to trace the identity of the subject in the event of results of clinical relevance;
- In the case of biological samples taken from minors, consent must be given by the parents and, upon reaching the age of majority, a new consent must be requested from the subject for their conservation and use, unless they are anonymized.

Considering the urgency and importance of biomedical research for humanity in the context of the pandemic, it is important to encourage the use for clinical research purposes of biological or clinical material residual from previous diagnostic or therapeutic activities.

This should be done defining homogeneous criteria for the use of biological samples, taking into account the procedures for accessing and acquiring the patient's consent on the subsequent use of the sample taken. It is to be hoped that the consensus on biological samples in the context of the COVID-19 pandemic will be broad, that is, open to future uses of the samples for research.

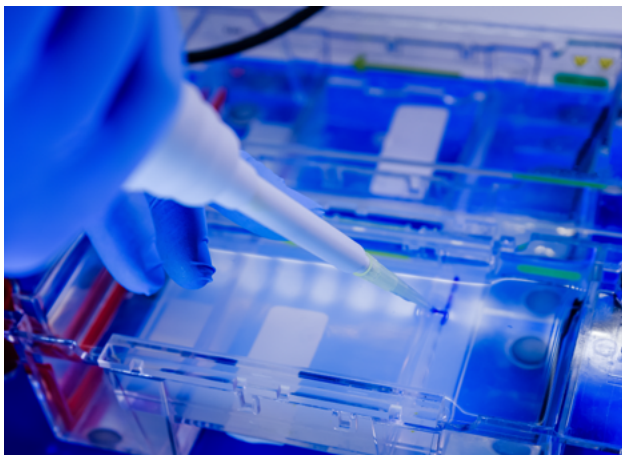
The legal status of biological samples has been problematic since their storage became possible. One of the central issues that has been discussed is that identity is biological as well as relational (so should be the legal status of these samples, some argue).

Should donation then be casually permitted? Given that each biological sample is also linked to our relationships (family, ethnic group, etc.) this is problematic and strongly connects the notion of informed consent to the concept of relational autonomy.

Another delicate issue is whether or not we should have a right not to know. Once more, the response to such a question is related to the interpretation we give to autonomy.

- A first interpretation is that of negative liberty – the freedom from interference from others.
- A second interpretation sees a moral agent that must always have sovereignty over their life/body but needs to know as much as possible -this means a duty to know.
- A third interpretation focuses on the importance of existential freedom (authenticity).

The first and third options allow for the right not to know, while the second does not.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Privacy, blanket consent and data

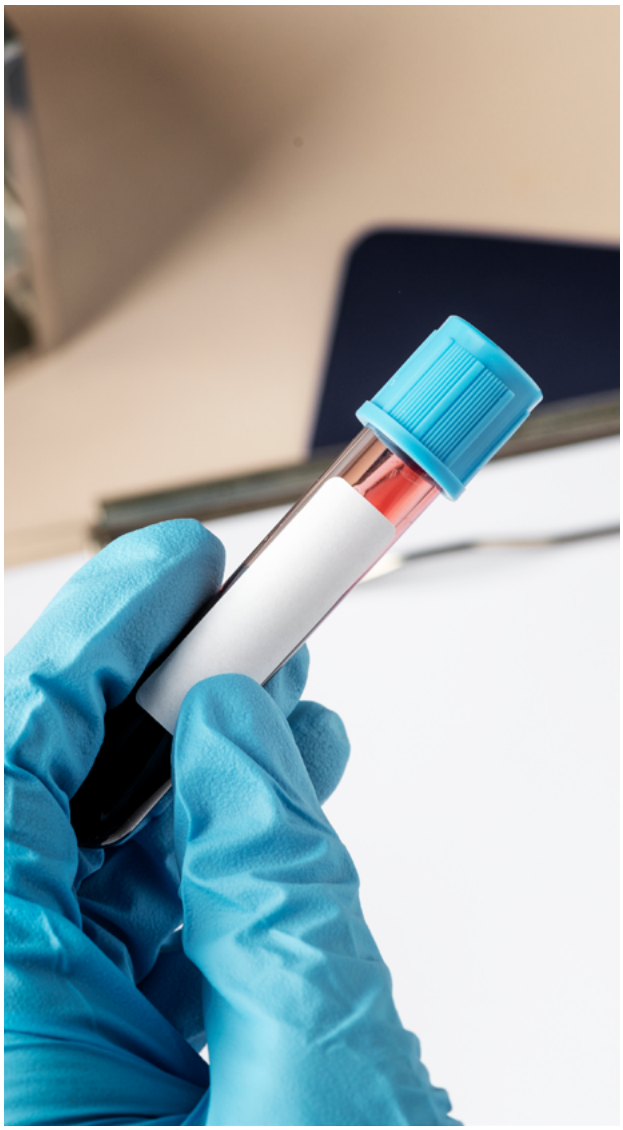
Clinical experimentation in emergency situations also concerns the issue of privacy. At a European level, the relationship between clinical trials regulation and personal data protection regulation (which tends to place less emphasis on the importance of individual informed consent) has become closer than previously -and COVID-19 has had an impact on that. For example, the GDPR has "freed" research in a sense (with broader and more all-encompassing consents called "blanket consent") and this seems to be more and more the way forward for clinical trials. We can give broad and selective consents (giving consent for e.g., public research, etc.), but in a less all-embracing way that would slow down or interrupt research.

With the advancement of technology, the collection of data can now be done remotely as well as on site and, obviously, the former option has increased drastically due to COVID-19. For example, in the US the FDA requested their employees to move their working time from on site to remote. To make such a change is important in times of pandemic, but we also need to understand what this shift can imply for the scientific validity of the trials.

Hacking is the main threat. In the case of a trial with multiple sites, we should make sure that each site can follow new protocols, because otherwise there is a risk of losing data or control of data if some sites are not able to comply with the requirements. If, for example some sites have outdated, unstable internet connections or easily hackable computers, this could put privacy at risk.

Finally, Data philanthropy (where private individuals or companies share data for the public good) opens the door to clinical trials and beyond as the whole paradigm of owning one's data will change further as a result of the pandemic.

Data sharing -the practice of sharing data used for research (scholarly, marketing or otherwise) to other investigators- has recently gained attention, in particular in relation to the issue of transparency (or lack thereof) concerning such sharing. Data sharing might also come under stress within the EU as different countries could have different levels of security and this aspect has become particularly relevant in relation to privacy.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

FACT SHEET XIV.
COVID-19 CLINICAL TRIALS AND PATIENTS' VULNERABILITIES

Minors

- In COVID-19 minors have been less affected, and those infected less seriously ill, so that the need for trials were not as urgent as in adults. However some children developed severe disease, so completely excluding these vulnerable populations from clinical trials, could exclude them from therapies.
- Multicenter coordinated trials should be prioritized. These would support sufficiently powered studies to test therapies for sicker, hospitalized children and facilitate analyses amongst subgroups with specific predisposing conditions. Existing trial networks like the Pediatric Trial Network could be enlisted. Some therapeutics trials in adults could be extended to include children, as a small number of studies are already doing. Joint studies also would enable resource sharing, alleviating pragmatic barriers to pediatric trials.
- Children receiving drugs for COVID-19 should at least be offered the opportunity to participate in prospective observational studies. Although these studies are limited in their ability to establish efficacy, they would allow prospective data collection on clinical and virological and drug-associated adverse effects. It would also permit comparative subgroup analyses between groups of children with varying risks for adverse outcomes. Conducting controlled, coordinated pediatric trials is the only way to learn whether the potential benefits of these drugs outweigh their risks.

Women

- The "protection by exclusion" of pregnant women from drug development and clinical therapeutic trials, even during pandemics, is not unprecedented. Even during the Ebola virus epidemic, pregnant women were excluded from all therapeutic and vaccine-development trials. This automatic disqualification denies pregnant women the potential for benefit given to other patients.
- The lack of data specific to pregnancy will negatively affect the health of pregnant women and their access to interventions in the current pandemic and beyond. This will create a knowledge gap concerning the safety and efficacy of any drugs or interventions that may emerge from current COVID-19 research. Although fetal safety is the most cited reason for the exclusion from research studies of pregnant women and those who could become pregnant, it is unethical to automatically preclude them from carefully designed clinical therapeutic research studies.
- Pandemics are underlining a cultural shift within the research community to view this population as in need of more evidence, particularly in pharmaceutical research. Pregnant women should be permitted to determine their eligibility and entry into a research study, always based on the principle of informed consent.
- Although one must consider the safety of a drug in pregnancy, it is equally important to consider the risks of not treating or inadequately treating pregnant women. Similarly, the risk of treatment to the fetus needs to be weighed against the risk of inadequate treatment, given that many of the conditions that affect the mother will ultimately adversely affect the fetus if not treated.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Patients coming from different cultural backgrounds

- Recruitment strategies and information provision approaches that work for the majority population may be ineffective for minorities. Interpreters, translators and cultural mediators could be needed, along with culturally sensitive recruitment methods.
- Ensuring research is culturally and linguistically accessible and inclusive requires the commitment and resources of researchers from the start. The COVID-19 pandemic has exposed a problem that has been known for a long time.
- Results of research must apply to everyone in the community who will be a candidate for treatment or prevention; researcher should ensure that groups, which are in the minority in a country because of their ethnic origin or some other way are not excluded. If research fails to engage all those who could benefit, there is no guarantee that the results will apply to populations not included in the research.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL I.
HOW TO BECOME A GOOD COMMUNICATOR

Effective communication is a skill all healthcare professionals need. It matters not only "what" is said but also "how" and by "whom". In a single day, healthcare professionals may speak to people of varying educational, cultural and social backgrounds and they must do so in an effective, caring and professional manner to convey the message and contribute to a participant's autonomy and understanding of the process.

Here are some key elements to consider:

Consider your environment	Time and place: • Approaching a participant in a confusing area with lots of people can hinder communication, and therefore participant's comprehension of the delivered information • Being in a chaotic place may require you to raise your voice which may have a negative impact: intimidation/lack of effective communication and consequently altering free consent • If you are going to be asking personal questions, finding a more private environment is essential to safeguard the privacy of the participant.
Building rapport	Listen and ask questions: • Listening without interrupting is vital, as it conveys interest and respect for another's point of view. Maintain eye contact to keep attention. • Use questions beginning with 'why', 'what, 'when', 'where' and 'how'. Open-ended questions provide the most effective way of understanding another person. • Use the valuable time you have to open the discussion slowly.
Body language & non-verbal communication	Use positive body language: • Eye contact is important. • Keep your hands and arms in front of your body, without crossing them. • Relax your facial expressions to prevent from grimacing, twisting or pursing your lips, lifting your eyebrows, or scowling. • Tone can help de-escalate a distressed and angry participant. This is referred to as the 'emotional contagion effect', where your emotional state can affect how another person feels.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL I.
HOW TO BECOME A GOOD COMMUNICATOR

Inclusive communication	• Be patient: It is essential to always respect the participants and dedicate the right amount of time to allow them to express themselves, so to get the whole story. • Be mindful of your language: Using complicated medical terminology, or 'jargon', is not an effective way to communicate with any participant. Try to use language that is simple, clear and non-threatening, while remaining accurate. Base your language on the questions asked to you and the cognitive ability of the patient you are speaking with. • If an adult is not able to consent and the consent is given by a family member, their assent must always be respected. • Take into account participants' age and their level of understanding, and tailor your explanation to meet their needs. • Regarding older adults: Including the family is often a big part of communicating with older participants. Always try to keep them involved in the conversation. • Regarding children: Although the parents/guardians may ask most of the questions, it is important to include the child and obtain their assent when talking about procedures and their health.

Some recommendations about what to do and not to do during the consent process, from a communication perspective:

DO:	DO NOT:
• Establish a positive relationship with the participant. • Make sure the participant feels comfortable to ask questions and clarify their understanding. • Provide trustworthy and clear information. • Use a plain and understandable language. • Use short sentences. • Receive appropriate training to ensure that verbal communication is delivered in a balanced and complete manner. • When children are involved, focus in both, the child and the parents.	• Overwhelm potential participants with extensive and complex study information. • Make gender-based assumptions. • Encourage participation, using undue influence (offering an excessive, unwarranted, inappropriate or improper reward or another overture for participating) or unjustified pressure (when people in a position of authority or with influence urge the subject to participate). • Use coercive language (presenting intentionally threat of harm to obtain compliance). • Employ vague expressions. • Use exculpatory language. • Use too technical or complex terms.

Note:
Remember to be careful to use neutral language when communicating with the participant.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL II.
HOW TO GAIN PARTICIPANTS' FEEDBACK

The experiences and opinions of potential and current participants can be useful in identifying unforeseen situations and ensuring that the informed consent process is adapted to the informational needs of the participants. This helps to define and improve the process of both ongoing and future studies, making informed consent a dynamic and evolving process.

It is recommended to have a de-briefing session with your team about the consent process using this information. Doing this after the study may help to improve the consent process of future studies, while doing it during the study may help improve the process of the current ones.

How to get the feedback?

- Consider different ways of obtaining feedback from study participants such as via surveys or comment boxes, both in electronic or physical formats. The tool used, and the conditions of its use, must be included in the study protocol and receive approval by the ethics committee.
- Choose the most appropriate mechanism by considering factors such as the participants' personal and social situation and their daily schedule.
- Feedback should be obtained at all stages, i.e. about the experience before starting the study (to get during the first month), during the study (to get during trial progress) and at the end of the study (to get during the last visit).
- Feedback should be obtained in a way that avoids overloading investigators and/or participants.
- The chosen tool should be made available in the participant's language, and the participant should also be allowed to give feedback in their native language.
- Include some free-text boxes so the participant can add any further information they consider relevant.

Example

If you do not have your own questionnaire, i-CONSENT recommends the use of the following toolkit:

- The Study Participant Feedback Questionnaire toolkit (by Transcelerate Biopharma)[27]: includes three short, validated surveys designed to capture feedback from participants anonymously at the beginning, during and end of the trial.

27. Study Participant Feedback Questionnaire Toolkit - TransCelerate [Internet]. TransCelerate BioPharma Inc. [cited 2021 February 23]. Available from: https://www.transceleratebiopharmainc.com/assets/patientexperience/study-participant-feedback-questionnaire/

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL III.
GUIDANCE ON CREATING "THANK YOU" LETTERS

A "Thank You" letter expresses gratitude from the investigation team and the sponsor. It is recommended that letters are prepared by the sponsor together with the investigators.

HOW TO PREPARE A THANK YOU LETTER?

- Personalise the letter.
- Highlight the importance of participation in research and the objectives that each participant is helping to reach.
- If possible, include information about the study and a summary of the available results.
- Explain how and when they will be informed about which treatment they received (if applicable).
- Remind participants of their right to access study results: inform them about how to access this information and approximately when it will be available.
- Provide contact details to the participant, in case they would like further information in the future.

WHEN AND HOW TO DELIVER IT?

- Usually, the principal investigator is responsible for sending the letter to the participant, on behalf of all the staff involved and the study sponsor, at the end of their participation in the study.
- It should not be delayed by the results of the study, as it can take several months for results to become available.
- It may be delivered in a number of different ways, such as in person, sent by postal mail, electronic mail or via a notification within a mobile application for the study; always taking into consideration the appropriateness from a social, methodological, legal and ethical point of view.

EXAMPLE:

There are templates in English and other languages such as the ones developed by Transcelerate Biopharma or by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL IV.
CREATING A SUMMARY OF THE RESULTS FOR LAYPERSONS

The EU Clinical Trial REGULATION (CTR) [REGULATION (EU) 536/2014] requires sponsors to provide summary results of clinical trials in a format understandable to laypersons. This is good practice for all clinical studies and not only clinical trials.

Specifically, participants in clinical studies want to know about the results of the studies they have contributed to, for themselves, their quality of life and society in general. The delivery of this information may influence their satisfaction with the study and their likelihood of participating in future studies.

Contents

The summary of the results of the clinical trial for laypersons according to Annex V of the CTR shall contain:

1. *Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);*
2. *Name and contact details of the sponsor;*
3. *General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);*
4. *Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);*
5. *Investigational medicinal products used;*
6. *Description of adverse reactions and their frequency;*
7. *Overall results of the clinical trial;*
8. *Comments on the outcome of the clinical trial;*
9. *Indication if follow up clinical trials are foreseen;*
10. *Indication where additional information could be found.*

Tips to prepare the summary

- Write the summary and reflect data and findings in an objective way (e.g. instead of "this study proved..." use "this study found that..."; or instead of "X is better than Y" use "# of people with treatment X experienced Y").
- Involve participants, patient groups or members of the public in the development and review of the summary. Incorporate health literacy concepts.
- Consider other formats, as well as written, for providing a summary and choose one that best suits the characteristics of the target population.
- The EU also provides recommendations[28] for the implementation of cited Regulation.
- Transcelerate has developed an implementation guide[29] for preparing Layperson Summaries of Clinical Trials.

OTHER RELATED FACT SHEETS:

FACT SHEET II. PRESENTING STUDY INFORMATION

TOOL V. METHODOLOGIES AND TOOLS TO INCORPORATE THE PARTICIPANT PERSPECTIVE

TOOL VI. FAKE NEWS AND THE RELIABILITY OF SOURCES

28. Summaries of Clinical Trial Results for Laypersons Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. 2018. [cited 2021 February 23]. Available from:https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf

29. Layperson Summaries of Clinical Trials: An Implementation Guide [Internet]. TransCelerate BioPharma Inc. [cited 2021 February 23]. Available from: http://www.transceleratebiopharmainc.com/wp-content/uploads/2017/02/Implementation-Recommendations_20Jan17_Final.docx

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL V.
METHODOLOGIES AND TOOLS TO INCORPORATE THE PARTICIPANT'S PERSPECTIVE

To gain insights from the community, the i-CONSENT project used a variety of interdisciplinary, mixed research methods, which ensured that the informed consent process was co-created by a team that included representatives from all the different roles in the recruitment process, particularly potential participants.

1. Why is it important to include the participant perspective?

As highlighted by EFPIA[30], in the past, decisions about participants in medical research were taken without their involvement. This led to inefficiencies in process and outcomes. Therefore, many companies are now developing new ways to incorporate participants' insights and to collaborate with them in an ethical way. This has improved trials, engagement, communication and participants' experiences.

2. How to include the participant's perspective for a better informed consent?

As part of the i-CONSENT project, the team has created a series of consent materials, with input from participant representatives. Feedback has been collected in the following ways:

1. Social media analyses: combining the skills of communication specialists, data scientists, and epidemiologists to analyse:
   - Facebook users opinions and feedback through posts on an OPBG hospital page and Facebook paid advertisements.
   - Public comments on news stories on vaccination were analyzed both qualitatively and quantitatively, using Natural Language Processing.
2. Online survey: We polled an extended network of clinical trial investigators to gain insights on their attitudes and practice on the use of informed consent
3. Design Thinking: We engaged patients and their families, investigators, social scientists, and cultural mediators from the initiation of the design process to:
   - Identify the problem
   - Define it
   - Develop ideas to solve it
   - Develop prototypes of the solution

All of these methods provided insights that complement the existing knowledge base gained from relevant literature and helped to design and create the consent materials. A mixed method approach for gaining participant perspectives is recommended to adapt the informed consent process to the local community.

3. Where to get more information?

- About how to work with patient groups:
  - EFPIA provide some useful guidance: Working together with patient groups.
- For a summary about how mixed-methods research can help you expand your evidence base:
  - Shorten A, Smith J. Mixed methods research: expanding the evidence base. Evidence-Based Nursing. 2017;20:74-5.
- For guidance on analysing information from different sources in a way that adds value:
  - Hussein A. The use of triangulation in social sciences research: Can qualitative and quantitative methods be combined? Journal of Comparative Social Work. 2009;1:1-12.
- i-CONSENT experience using Design Thinking.

30. EFPIA Patient Think Tank. Working together with patient groups. 2017.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

TOOL VI.
FAKE NEWS AND THE RELIABILITY OF SOURCES

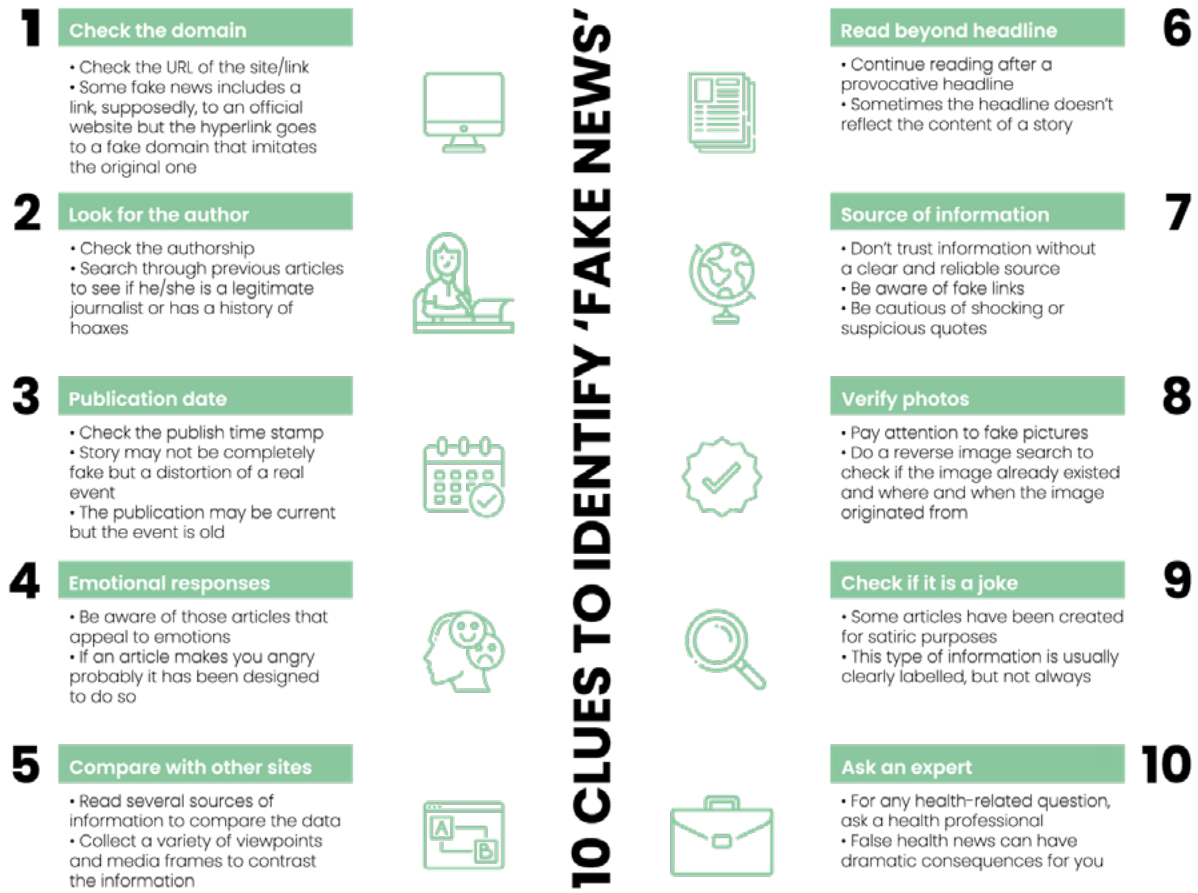
Fake health news can have dramatic consequences for participants and is a significant concern in today's society. It can have negative consequences, particularly in the fields of politics and health, and impact individual and societal perceptions and actions.

There are different definitions and classifications for the expression "fake news". A much-quoted classification is by media professor Melissa Zimdars of Merrimack College[31], who groups "fake news" into four categories, although each can be grouped in more than one category:

- Fake, false, or regularly misleading websites, pictures, videos or articles shared on social media.
- Websites, pictures, videos or articles circulating misleading and/or potentially unreliable information or presenting opinion pieces as news.
- Websites, pictures, videos or articles that sometimes use hyperbolic or clickbait headlines and/or social media descriptions, but which circulate reliable and/or verifiable information at other times.
- Satire/comedy sites, pictures, videos or articles that have the potential to be shared as actual news.

This factsheet offers a tool that investigators can use to prevent participants from being misled by "fake news" and help them to improve their health literacy.

10 tips for identifying "Fake News" or unreliable sources



31. Zimdars M. False, Misleading, Clickbait-y, and/or Satirical.: "News" Sources.; 2016 [Available from: http://d279m997dpfwgl.cloudront.net/wp/2016/11/Resource-False-Misleading-Clickbait-y-and-Satirical-"News"-Sources-1.pdf; Last visit: 4th of October 2020]

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

4. LIST OF I-CONSENT'S SCIENTIFIC DELIVERABLES & PUBLICATIONS

Scientific deliverables and publications' elaboration was ongoing when the guidelines where released. Find the full scientific deliverables and publications list at CORDIS.

Deliverables

- WP1: A multi-layered approach to informed consent.
  - D1.1. Report on guidelines, standards and initiatives for improving informed consent in the healthcare context.(https://i-consentproject.eu/wp-content/uploads/2019/01/D1.1-Report-on-guidelines-standards-and-initiatives-for-improving-informed-consent-in-the-healthcare-context.pdf).
  - D1.2. Report on gender and age-related issues associated with the acquisition of informed consent. (https://i-consentproject.eu/wp-content/uploads/2019/01/D1.2-Report-on-gender-and-age-related-issues-associated-with-the-acquisition-of-informed-consent.pdf).
  - D1.3. Ethical and legal review of gender and age-related issues associated with the acquisition of informed consent. (https://i-consentproject.eu/wp-content/uploads/2019/02/D1.3_EthicalLegal_20171030_FINAL.pdf).
  - D1.4. Ethical issues concerning informed consent in translational / clinical research and vaccination. (https://i-consentproject.eu/wp-content/uploads/2019/01/D1.4-Ethical-issues-concerning-informed-consent-in-translationalclinical-research-and-vaccination.pdf).
  - D1.5. Legal issues concerning informed consent in translational/clinical research and vaccination. (https://i-consentproject.eu/wp-content/uploads/2019/01/D1.5-Legal-issues-concerning-informed-consent-in-translationalclinical-research-and-vaccination.pdf).
  - D1.6. Patient group insights on improving guidelines for informed consent, including vulnerable populations, under a gender perspective. (https://i-consentproject.eu/wp-content/uploads/2019/01/D1.6-Patient-involvement-in-vaccine-research.pdf).
  - D1.7. Socio-cultural, psychological and behavioural perspectives toward informed consent process. (https://i-consentproject.eu/wp-content/uploads/2019/01/D1.7-Sociocultural-psychological-and-behavioural-perspectives-towards-informed-consent-process.pdf).

32. More deliverables and papers will be published in the framework of the Project after the publication of the guidelines. Find them in: https://i-consentproject.eu/results/ or https://cordis.europa.eu/project/id/741856/results

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Papers

- Monographic BioLaw Journal, Special Issue 1/2019: 1-149.
  - L. Palazzani. Why informed consent requires attention once more?
  - J. Fons-Martínez, C. Ferrer-Albero, R. Russell, E. Rodgers, L. Glennie, J. Díez-Domingo. i-CONSENT: presentation of the project and the importance of participants' perspective in the informed consent process.
  - L. Palazzani. Informed consent, experimentation and emerging ethical problems.
  - F. Macioce. Informed consent procedures between autonomy and trust.
  - J. Fons-Martínez, F. Calvo Rigual, J. Díez-Domingo, L. Nepi, L. Persampieri, C. Ferrer-Albero. Contents of the minor's assent in medical research: differences between the scientific literature and the legal requirements.
  - L. Nepi. Ethical issues concerning the informed consent process in paediatric clinical trials: European guidelines and recommendations on minor's assent and parental permission.
  - L. Persampieri. Gender and informed consent in clinical research: beyond ethical challenges.
  - A. Garcia, M. Garasic. Interreligious perspectives on Informed consent in the light of Human Rights.
  - L. Palazzani, F. Macioce, M. Daverio, V. Ferro, L. Persampieri. New strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials.
  - M. Daverio. Informed Consent in translational/clinical research. Ethical issues according to international guidelines.
  - V. Ferro. The impact of socio-cultural and religious background in the ICP. Implications for sensitive recruitment of multicultural participants in CT.
- Studia Bioethica. (2919). 11(2): 3-57.
  - E. Zhang. Informed consent – A Critical Response from a Buddhist Perspective.
  - L. Palazzani. Multicultural and interreligious perspectives on informed consent. The Christian perspective.
  - M. Garasic, A Garcia. New Considerations on Informed Consent.
  - R. Fan. A Confucian View of Informed Consent and the Issue of Vaccination.
  - A. Padela. Reflecting and Adapting Informed Consent to fit within an Islamic Moral Landscape and in Muslim Contexts.
  - D. Heyd. Informed Consent and Clinical Trials - A Jewish Perspective.
  - A. Lavazza. A Neurobioethical Perspective on Informed Consent.
  - E. Sirgiovanni. Agency, autonomy and consent: cues from the neuroscience of self-control.
- Medicina y Ética 2019. 30(2): 621-635.
  - A. García Gómez; M.D. Garasic; M. Cubillo Díaz-Valdés. Ethical issues concerning informed consent in translational/clinical research and vaccination bias and informed consent.
- Biolaw journal 3/2020:323-335.
  - L. Palazzani. Consenso informato alla ricerca clínica nell'ambito della pandemia CoViD-19: tra bioetica e biodiritto.
- Frontiers in Pediatrics 2021. 8:520803.
  - Jackson SM, Daverio M, Perez SL, Gesualdo F and Tozzi AE. Improving Informed Consent for Novel Vaccine Research in a Pediatric Hospital Setting Using a Blended Research-Design Approach.
- BMC Medical Ethics volume 22, Article number: 18 (2021)
  - Francesco Gesualdo, Margherita Daverio, Laura Palazzani, Dimitris Dimitriou, Javier Diez-Domingo, Jaime Fons-Martinez, Sally Jackson, Pascal Vignally, Caterina Rizzo & Alberto Eugenio Tozzi. Digital tools in the informed consent process: a systematic review.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Chapters in Books & Books of Abstracts.

- 5º Congreso de la Asociación Nacional de Comités de Ética de la Investigación (ANCEI): Los Comités de Ética de la Investigación: conjugando la utilidad social de la investigación, los cambios normativos y las nuevas tecnologías. Valencia, Spain, May 17-18, 2018. (https://ancei.es/wp-content/uploads/2019/10/Libro-de-ponencias-y-comunicaciones-V-CONGRESO-ANCEI-2018.pdf).
  - J. Fons-Martínez, F. Calvo Rigual, J. Díez-Domingo, L. Nepi, L. Persamperi, C. Ferrer Albero. Contenido del asentimiento del menor en investigación médico: diferencias entre la literatura científica y el requisito legal. Pp. 129- 133.
  - F. Calvo Rigual, J. Fons-Martínez, J. Díez-Domingo, C. Ferrer Albero. La comprensión de los documentos de asentimiento en investigación con menores: una revisión sistemática. Pp. 189-194.
- 6º Congreso de la Asociación Nacional de Comités de Ética de la Investigación (ANCEI): Trabajando juntos para mejorar el debate ético en la investigación biomédica. Tarragona, May 30-31, 2019. (https://ancei.es/wp-content/uploads/2019/10/Libro-de-ponencias-y-comunicaciones-VI-Congreso-ANCEI-2019.pdf).
  - J. Fons-Martínez, C. Ferrer-Albero, R. Russell, J. Díez-Domingo. Proyecto i-CONSENT: desarrollo de guías para mejorar el proceso de elaboración de consentimientos informados implicando a todas las partes interesadas en el proceso de investigación. Pp. 3-8.
  - J. Fons-Martínez, A.J. Quesada, E. Fernández de Uzquiano, M. Ugalde Díez, A. Hernández Gil, M. Cubillo Día-Valdés. El uso de las redes sociales para el reclutamiento de participantes en ensayos clínicos: perspectiva de los comités de ética (CEI/CEIm). Pp. 77-82.
  - J. Fons-Martínez, M. Cubillo Día-Valdés, C. Ferrer-Albero, J. Díez-Domingo. La perspectiva de género en el proceso de consentimiento informado en investigación médica. Pp. 145-150.
  - J. Fons-Martínez, M. Cubillo Díaz-Valdés, R. Russell, C. Ferrer-Albero, J. Díez-Domingo. El proceso de consentimiento informado en investigación clínica: propuesta del proyecto i-CONSENT. Pp. 151-156.
- 36th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). Malmo, Sweden, May 28-June 2, 2018 (https://keneswp.azureedge.net/wp-content/uploads/sites/21/2018/08/ESPID-2018-Abstracts.pdf).
  - C. Ferrer-Albero, F. Calvo-Rigual, J. Fons-Martínez, J. Díez-Domingo. Information, Comprehension and Competence: Key elements in children's assent for vaccine research (ESP18-0781).
- 38th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). Virtual Meeting, October 26-29, 2020 (https://keneswp.azureedge.net/wp-content/uploads/sites/77/2020/11/ESDID-2020-Abstracts.pdf).
  - D. Dobreva, J. Fons-Martinez, C. Ferrer-Albero, S. Jackson, J. Diez-Domingo. Design thinking as a process to improve the communication of information to children (P0441 / #1444).
- III National Congress of Young Researchers in Biomedicine. Valencia, April 24-26, 2019.
  - J. Fons-Martínez, J. García-Bayarri, J. Díez-Domingo. How to strengthen the recommendations for the informed consent process in health-related studies: The i-CONSENT project methodology. Pp. 59. (https://i-consentproject.eu/wp-content/uploads/2019/05/BookOfAbstracts_ConBioPreVal2019.pdf).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

- Good Health, Quality Education, Sustainable Communities, Human Rights: the scientific contribution of Italian UNESCO Chairs and partners to SDGs 2030 (https://www.fupress.com/archivio/pdf/3951_20122.pdf)
  - A. García Gómez, M.D. Garasic. Dilemmas of informed consent process in clinical research from a multireligious perspective. Pp. 47-56.
- XII Congreso Internacional de la Asociación Española de Boética y Ética Médica. Valencia, Spain, October 25-26, 2019. (http://aebioetica.org/revistas/2019/30/100/331.pdf)
  - M. Cubillo Díaz-Valdés, C. Ferrer-Albero, J. Fons-Martínez, R. Boceta Muñoz, O. Martinez Casares, D. Dimitriou. El concepto terapéutico errado en ensayos clínicos. Cuad Bioet. 2019;30(100):341.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 741856

Consortium members:

ANEXO 8: How Spanish biobanks have adapted the informed consent process during the COVID-19 pandemic.

Special issue

How Spanish biobanks have adapted the informed consent process during the Covid-19 pandemic

Pablo Enguer-Gosálbez, Jaime Fons-Martínez, Jacobo Martínez-Santamaría, Ana María Torres-Redondo, Cristina Villena-Portella, Aurora García-Robles, Javier Díez-Domingo*

ABSTRACT: Due to the situation caused by the Covid-19 pandemic, biobanks have adapted, among other processes, the obtaining of informed consents (IC). This paper details the most relevant elements of the applicable regulations, describes the adaptations done by some of the biobanks of the Spanish Biobank Network to manage the IC process, which have been approved by their Ethics Committees, and draws some conclusions from the results obtained from the survey carried out on these biobanks.

KEYWORDS: Biobanks; bioethics; Covid-19; informed consent; Spain

SUMMARY: 1. Introduction – 1.1. The context of biobanks in Spain – 1.2. Key concepts relating to informed consent – 1.3. The management of informed consent according to Spanish legislation – 1.4. The position of the main international and national organizations on the informed consent process during the Covid-19 pandemic – 1.5. The importance of Ethics Committees for the approval of protocol changes – 2. Methodology – 3. Results and discussion – 4. Conclusions.

1. Introduction

On January 31, 2020, the World Health Organization (WHO) declared the outbreak of Covid-19 infection as a public health emergency of international importance, which they raised to an international pandemic on March 11, 2020. In Spain, this circumstance led to the establishment of a state of national alarm on two occasions, in accordance with the measures provided for in two Royal Decrees[1,2].

* *Pablo Enguer-Gosálbez: IBSP-CV Biobank and Valencian Biobanking Network, FISABIO-Public Health, Valencia. E-mail: enguer_pab@gva.es; Jaime Fons-Martínez: Vaccine Research Area, FISABIO-Public Health, Valencia. E-mail: fons_jai@gva.es; Jacobo Martínez-Santamaría: IBSP-CV Biobank and Valencian Biobanking Network, FISABIO-Public Health, Valencia. E-mail: martinez_jac@gva.es; Ana María Torres-Redondo: Biobank of the Ramón y Cajal University Hospital-IRYCIS, Madrid. E-mail: atorres.plataforma@gmail.com; Cristina Villena-Portella: Centro de Investigación Biomédica en Red - Respiratory Diseases, CIBERES Pulmonary Biobank Consortium, Hospital Universitari Son Espases, Palma, and Spanish Biobank Network, Carlos III Health Institute. E-mail: cvillena@ciberes.org; Aurora García-Robles: Centro de Investigación Biomédica en Red - Respiratory Diseases, CIBERES Pulmonary Biobank Consortium, Hospital Universitari Son Espases, Palma, and Spanish Biobank Network, Carlos III Health Institute. E-mail: coordinacion.rnbb@gmail.com; Javier Díez-Domingo: Vaccine Research Area, FISABIO-Public Health, Valencia. E-mail: jdiezdomingo@gmail.com.* *The essay has been developed in the framework of the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), project funded by the European Union framework program H2020 (Grant Agreement n° 741856). The article was subject to a double-blind peer review process. The Authors thank the Reviewers for their comments.*

[1] Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por la infección Covid-19 (BOE no. 67, of March 14, 2020).

[2] Real Decreto 926/2020, de 25 de octubre, por el que se declara el estado de alarma para contener la propagación de infecciones causadas por el SARS-CoV-2 (BOE no. 282, of October 25, 2020).

The pandemic has generated a major health crisis due to the high number of infected people, who pose a risk to the health of the population as a whole, and due to the high number of people who need health care, and with relative frequency, hospitalization and critical care, leading to a saturation situation of hospital emergencies and Intensive Care Units. In order to mitigate this situation and reduce the risk of contagion of the disease, when the first state of alarm was decreed, extraordinary measures of different kinds were adopted and applied to the entire population and, in particular, to those affected. On the other hand, emergency measures were also established to face the economic and social impact of Covid-19, including measures to support research on the infection. Thus, the activity of biobanks has been intensified due to an increase in the number of requests for samples, specifically from Covid-19 infected subjects, for use in research projects on the disease. The adaptation of biobanks to this new reality depends, among other factors, on the following ones[3]:

- Human resources (on-site or remote work) and material resources (facilities, equipment and security measures) available.
- The biosecurity guidelines established by the institution to which they are attached.
- The degree of difficulty of obtaining informed consent (IC) by a healthcare staff swamped with a lot of work, taking into account that the usual procedure for obtaining IC involves the signature of the patient (or legal representative, if applicable) and the reporting staff (health professionals).
- The different sources of the samples (surplus / expressly collected samples).
- The quantity, variety and time of collection of the samples to be stored.

Under these circumstances, biobanks are facing, when managing samples from patients with Covid-19, with situations that require a rethinking of the system to be used for the inclusion of samples and obtaining the IC.

1.1. The context of biobanks in Spain

Before addressing this issue, it is worth explaining what biobanks are like in Spain, since their governance, organizational characteristics and sources of funding are different in each European country[4]. In the case of Spain, biobanks for biomedical research purposes are regulated by the *Ley 14/2007, de 4 de julio de investigación biomédica* and the *Real Decreto 1716/2011, de 18 de noviembre*, which develops the mentioned Law. Biobanks are part of the strategic agendas of the National Health System for the promotion and improvement of public and universal healthcare. In fact, the rules that regulate them highlight their "vocation of public service", although it also defines them as "public or private, non-profit establishments that host a collection of biological samples (of human origin) conceived for diagnostic or biomedical research purposes, and organized as a technical unit with quality, order and destination criteria"[5,6]. Thus, a biobank must have a defined structure, a

[3] Spanish Biobank Network, *Gestión por los biobancos de la Red Nacional de Biobancos de la obtención de los consentimientos informados ante la pandemia para investigación sobre el SARS-CoV-2 y la enfermedad Covid-19* (Comité Asesor Ético-Legal, April 2020).

[4] I. MEIJER, J. MOLAS-GALLART, P. MATTSSON, *Networked research infrastructures and their governance: The case of biobanking*, in *Science and Public Policy*, 39 (4), 2012, 491-499.

[5] Ley 14/2007, de 3 de julio, de Investigación biomédica (BOE no. 159, of July 4, 2007).

[6] Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras

scientific direction and a written operating regulation. As is logical, its main function is to provide quality samples to the scientific community.

These rules establish the authorization system for the constitution and operation of biobanks, which must be authorized by the Autonomous Communities and registered in the Spanish Biobank Register of the *Instituto de Salud Carlos III* (ISCIII). There are currently 75 biobanks authorized in Spain for biomedical research purposes.

The ISCIII, a Spanish organization of international reference in the field of Public Health and Biomedical Research, created, in 2009, the Spanish Biobank Network with the aim of providing high-level scientific, technical and technological support to R+D+i projects in science and health technologies, as well as encouraging innovation in health technologies, by supplying high-quality human biological samples and associated data.

During the last years, the efforts of this network, formed by 39 members, have focused on working in a coordinated but decentralized way, and on creating a catalogue of samples and a single window for sample requests. Although Spain is not a member of the European research infrastructure for biobanks BBMRI-ERIC (https://www.bbmri-eric.eu/), this organization has served as a model to define the work of Spanish biobanks and reconfigure their practices[7]. This fact confirms that, in the case of biobanks, governance tends to be based on guidelines and international collaboration, rather than on state or government action[8].

Since the beginning of the pandemic, the Spanish Biobank Network has played a key role in the coordination of national biobanks, by holding weekly informative meetings, preparing guides and recommendations for the management, collection and conservation of biobank samples from patients affected by Covid-19, to ensure their later usefulness both in terms of quality and integrity as well as the ethical-legal guarantee with respect to current regulations[3,9], and creating a national repository of clinical information associated with samples from patients affected by Covid-19 admitted at different stages of the disease. This information includes epidemiological and clinical aspects, biological markers, treatments and comorbidities, in short, data of interest for detailed knowledge of the characteristics of the patients.

Similar experiences are happening at the European and international level. The International Society for Biological and Environmental Repositories (ISBER) has fostered collaboration between countries to analyze the impact of the pandemic on biobanks globally, while the BBMRI-ERIC has organized two webinars that have helped to continuously monitor the evolution of the pandemic at the international level.

1.2. Key concepts relating to informed consent

The world is living in a reality in which it is necessary to establish a balance between reducing obstacles that appear during the conduct of an investigation, in search of efficiency in terms of time

biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica (BOE no. 290, of December 2, 2011).

[7] V. ARGUDO-PORTAL, M. DOMÈNECH, *The reconfiguration of biobanks in Europe under the BBMRI-ERIC framework: towards global sharing nodes?*, in *Life Sciences, Society and Policy,* 16:9, 2020.

[8] A.C. DA ROCHA, *Biobancos, cultura científica y ética de la investigación*, in *Dilemata*, 4, 2010, 1-14.

[9] Spanish Biobank Network, *Guía de la Red Nacional de Biobancos para el manejo de muestras humanas en investigación biomédica. Recomendaciones ante la pandemia de Covid-19* (April 2020).

and needs, and the guarantee of its methodological rigor. Depending on whether one or the other of these aspects is given more importance, four types of IC can be considered[10]:

- Specific/closed consent. The donor gives consent for a specific research project. Therefore, it is not possible to carry out secondary research derived from samples stored in biobanks, since at the time of donation there is no information on the future research in which the sample will be used. The solution would be to ask donors for new consent to use the sample previously stored in the biobank, although this can be annoying for them and ineffective for research, and end up causing a reduction in the number of available participants.
- Broad consent. The donor gives consent not only for specific studies, but also extends the acceptance to any class or line of research that the biobank deems appropriate. In this way, advances in research are facilitated.
- Blanket/open consent. The donor gives consent, without restrictions regarding the scope and duration of the research, for any future use of his biological sample and its associated clinical data, including forensic and commercial uses. This type of consent requires minimal administrative and organizational effort. It is used by most genetic data biobanks.
- Dynamic consent. This consent is based on the use of modern communication strategies (computer tools) to inform, involve, offer options and obtain consent for each of the research projects that may be derived from a biological sample. This is a model of continuous two-way communication between donors and researchers, thus overcoming the ethical problem that passive participation implies. It generates greater trust on the part of donors in the research, since participants have control over the use of their biological samples and associated clinical data.

Given these possibilities, it should be noted that there are two different approaches that guarantee the privacy of personal data associated with biological samples and with other relevant data from a public health point of view:

- Anonymization, or irreversible disassociation, which is defined as the "process by which it is no longer possible to establish by reasonable means the link between a piece of data (or a biological sample) and the subject to whom it refers" (art. 3.c) of the *Ley de Investigación biomédica*). This same law also defines, in art. 3.i), the anonymised or irreversibly disassociated data as that "data that cannot be associated to an identified or identifiable person as the nexus with all information that identified the subject has been destroyed or because such association demands a non-reasonable effort, understood as the use of disproportionate amounts of time, expense and work"[5].
- Pseudonymisation, or reversible disassociation, which is defined as that "processing of personal data in such a way that it can no longer be attributed to an interested party without using additional information, provided that said additional information appears separately and is subject to technical and organizational measures designed to guarantee that the personal data is not attributed to an identified or identifiable natural person" (art. 4.5 of Regulation (EU)

[10] N. SERRANO-DÍAZ, E. GUÍO-MAHECHA, M.C. PÁEZ-LEAL, *Consentimiento informado para Biobancos: Un debate abierto*, in *Revista de la Universidad Industrial de Santander. Salud*, 48(2), 2016, 246-256.

2016/679)[11]. This concept also appears in the *Ley de Investigación biomédica,* although with different terminology, since art. 3.k) defines the codified or reversibly disassociated data as that "data that is not associated to an identified or identifiable person as the information that identified that person has been substituted or detached using a code that allows the reverse operation"[5]. In simpler terms, pseudonymising consists of substituting one attribute for another in a record.

Thus, the anonymization can be considered absolute, since it is not possible to know, by reasonable means, the personal data that were originally processed. On the contrary, in the case of the pseudonymisation, the person responsible for the data could reverse the process in order to access the information subject to protection.
For all the above, it is recommended that the less restrictive the type of consent granted by donors is regarding the possible uses of the sample or the data, the greater security measures are used to preserve their identity.

1.3. The management of informed consent according to Spanish legislation

In Spain, the use of biological samples of human origin and associated data in biomedical research is currently regulated by three legal instruments[5,6,12] that include exceptional cases and special regimes that contemplate the adaptation of obtaining IC to the clinical situation of the subject, the pandemic situation and the need for research for public health reasons, and which have been taken into account to assess the situation in each biobank and decide how to proceed in this regard.
It is established that the "obtaining of biological samples for biomedical research shall be undertaken solely when the previous written consent has been obtained from the source subject". The requirements established by Spanish legislation for the generic IC model tallies with broad consent. This consent will also be essential when "the aim is to use biological samples for biological research that have already been obtained for a different purpose, irrespective of whether there is an anonymization"[5].
However, there are some exceptions to this obligation. "Codified or identified samples for biomedical research may be used without the consent of the source subject in situations of exceptional relevance and gravity for public health or when the obtaining of this consent is not possible or it entails a non-reasonable effort. In these cases, the favourable verdict of the corresponding Research Ethics Committee (REC) shall be necessary, which must take into account, at least, the following requisites[5,6]:

a) That the research is of general interest.
b) That the research is undertaken by the same institution that requested the consent for the obtaining of samples, if such consent is necessary.

[11] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Official Journal of the European Union L 119, 4.5.2016).
[12] Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (BOE no. 294, of December 6, 2018).

c) That the research is less effective or not possible without the identifying data of the source subject.
d) That there is no record of an express objection of the source subject.
e) That personal data is guaranteed confidentiality.
f) That there is no viable alternative to carry out the project with another group of samples for which consent is available."

Moreover, the *Ley Orgánica 3/2018, de Protección de Datos* adds that "health authorities and public institutions with powers in public health surveillance may carry out scientific studies without the consent of those affected in situations of exceptional relevance and severity for the public health". On the other hand, if the study is carried out by a research group, the consent of the subject for the secondary use of the data (study related to the initial research) can be dispensed with when the following conditions are met[12]:

- The data is pseudonymised.
- There is express authorization from the corresponding REC.

The Spanish legislation also regulates other aspects related to the management of IC by biobanks:

- Time of signing the consent (art. 60.1 and 60.2 of the *Ley de investigación biomédica* and art. 23.4 of the *Real Decreto 1716/2011*)
- Information prior to consent (art. 59 of the *Ley de investigación biomédica* and art. 23.2 and 23.3 of the *Real Decreto 1716/2011*)
- Confidentiality of the source subject (art. 59.1.h) of the *Ley de investigación biomédica*, additional provision 17.2.d) of the *Ley Orgánica 3/2018, de Protección de Datos* and art. 34.3 of the *Real Decreto 1716/2011*)
- Possible purposes of obtaining samples (art. 22.2 of the *Real Decreto 1716/2011*)
- Final destination of non-biobank samples (arts. 59.1.f) and 61.1 of the *Ley de investigación biomédica* and art. 27 of the *Real Decreto 1716/2011*)
- Use of samples from certain groups (art. 58.5 of the *Ley de investigación biomédica* and arts. 23.2.n) and 26.1 of the *Real Decreto 1716/2011*)
- Use of samples from other countries (art. 31 of the *Real Decreto 1716/2011*)

1.4. The position of the main international and national organizations on the informed consent process during the COVID-19 pandemic

In clinical practice, there may be situations in which it is not possible to obtain IC by the usual means and it must be requested by other means, such as orally, or even the need for the exemption of obtaining it should be considered. In fact, as early as 1964, the Declaration of Helsinki of the World Medical Association provided that, in the case of exceptional situations in which it is impossible or impractical to obtain consent for a research, it can only be carried out after being considered and approved by a REC[13].

[13] WMA, Declaration of Helsinki – Ethical Principles for Medical Research involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964.

The International Bioethics Committee (IBC) has indicated that, although the secondary use of health data requires a new specific consent, such rule finds an exception when procedures such as pseudonymisation are implemented, which prevents researchers or third parties from accessing personal data[14]. Another four requirements are added to this one (apparent public interest in the research; difficulty in obtaining a new consent; legal origin of the data; and evaluation by a REC).

The pandemic has highlighted the need to find choices to the usual ethical review procedures. In the current context, the Pan American Health Organization and the World Health Organization itself encourage the practice of broad consent for the use of samples and data in future research that is not planned yet but will probably be designed as new information emerges[15].

Along the same lines, the Bioethics Committee of Spain, in an emergency such as the current one, recommends authorizing the secondary use of health data and biological samples without requiring a new express consent from the source subjects or, in the case of deceased people, their legal representatives. It also emphasizes that the data and samples from health centers that have taken part in the treatment of patients infected with the SARS-CoV-2 virus should be considered, in general, of legal origin, as it is understood that the patients have given their consent to the treatment or any of the exceptions to consent provided by law has occurred[16]. In addition, it indicates that, for this secondary use without express consent to be reasonable, it must have a very relevant interest for the health of the community and enough guarantees must be implemented to prevent non-legitimized third parties from accessing the individual's identity through the data. As expressed above, this can be achieved through two different approaches: anonymization and pseudonymisation. The authorization of the corresponding REC is also necessary, as established in the additional provision 17.2 of the *Ley Orgánica 3/2018, de Protección de Datos*. The Bioethics Committee of Spain makes all these recommendations based on the legal regime applicable to these cases, which it explains in depth in section 3 of its report.

On the other hand, and although it does not directly affect the field of biobanks, the approach of the European Medicines Agency regarding the management of ICs for clinical trials during the pandemic is also relevant. This body has stated that "unless linked to the implementation of urgent safety measures, changes in IC procedures will need to be reviewed and approved by the relevant ethics committee in advance", and that "in case a sponsor plans to initiate a trial aiming to test new treatments for Covid-19, advice should be sought on alternative procedures to obtain IC, in case the physical consent cannot leave the isolation room, and therefore is not appropriate as trial documentation"[17]. And it adds that "if re-consent is necessary for the implementation of new urgent changes in trial conduct, alternative ways of obtaining such re-consent should be considered during the pandemic. These could comprise contacting the trial participants via phone or video-calls and

[14] International Bioethics Committee, UNESCO, *Report Of The IBC On Big Data And Health* (Paris, 15 September 2017).

[15] Pan American Health Organization (World Health Organization, Regional Office For The Americas), *Ethics guidance on issues raised by the novel coronavirus disease (Covid-19) pandemic* (Washington, D.C., March 16, 2020).

[16] *Informe del Comité de Bioética de España sobre los requisitos ético-legales en la investigación con datos de salud y muestras biológicas en el marco de la pandemia de Covid-19* (Madrid. April 28, 2020).

[17] European Medicines Agency, *Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic* (Version 3, 28/04/2020).

obtaining oral consents, to be documented in the trial participants' medical records, supplemented with e-mail confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants are back at the regular sites".

1.5. The importance of Ethics Committees for the approval of protocol changes

There is no single method that all Spanish biobanks can apply, it is difficult to establish a harmonized procedure for all of them. In any case, changes in the management of obtaining ICs must be endorsed by the opinion of the Ethics Committee to which the biobanks are attached (REC), which makes an assessment, taking into account the following aspects[3]:

- The implementing legislation. Apart from the three previously mentioned legal texts of state scope, it should be noted that, during the first state of alarm caused by Covid-19, only one of the seventeen autonomous communities that make up the country (Galicia) has specifically regulated the management of IC by biobanks during the health emergency period[18].
- The urgency of availability of samples for projects on Covid-19.
- The circumstances of each biobank.
- The inability of obtaining IC in a hospital by non-health staff.
- The infectious capacity of the physical IC document.
- The isolation of the admitted subjects and the severity of their condition, which affects their ability to consent.

Taking into account all these factors, RECs can choose from different decisions, ranging from authorizing total exemption from obtaining the IC to forcing consent to be obtained through the usual procedure, including intermediate options such as obtaining the IC in the near future or authorization of oral consent or in electronic format.
The role of the RECs is also essential in evaluating the requests for samples received by biobanks and the methodological, ethical and legal quality of research projects. This process is a new point of control and verification of compliance with the procedure that had been established to obtain ICs, always trying to guarantee respect for the fundamental rights of people, also and, specially, in times of health emergency[19].

2. Methodology

In order to better understand how the management of ICs by Spanish biobanks has worked since the Covid-19 pandemic began, an online survey (Annex) was carried out, the preparation of which was based, among other sources, in a report published by the Spanish Biobank Network in April 2020. The survey was sent to 43 biobanks from the coordination office of the network itself, a large majority of

[18] Orden de 2 de abril de 2020 por la que se aprueban medidas en materia de investigación sanitaria en los centros del Sistema público de salud de Galicia durante el período que dure la emergencia sanitaria por el COVID-19 (Diario Oficial de Galicia no. 68, of April 7, 2020).
[19] A. Cervera Barajas, M. Saldaña Valderas, *Investigación clínica y consentimiento informado en época de pandemia COVID-19. Una visión desde la ética de la investigación*, in *Medicina Clínica*, 2020.

ISSN 2284-4503

them being members of it. According to the Spanish Biobank Register, there are 75 biobanks authorized to act as such in Spain[20], so the number of biobanks to be surveyed represents a sufficiently representative sample to draw conclusions.
Although participation in the survey was voluntary, a thank you message was sent to all those biobanks that offered their collaboration. Biobanks had 9 calendar days (from March 8 to March 16, 2021) to answer the 13 questions posed in the survey.
At the beginning of the survey, the identification of the biobank that responded was requested. This request was made to check that a single answer had been obtained for each biobank. The scientific directors of the biobanks were informed of this point and warned that the data obtained would be published, in any case, anonymously and in an aggregate manner. The survey contained two filter questions (see survey in Annex):

- Question 2. If "No" was answered, the survey ended at that point;
- Question 7. If the answer was "Yes", then another question included in question 7 itself would appear. If the answer was "No", you would advance directly to question 8.

3. Results and discussion

Finally, the survey was answered by 36 of the 43 biobanks to which it was sent, which represents a participation rate of 84%. Considering that there are 75 authorized biobanks in Spain, the study includes information on almost 50% of the authorized Spanish biobanks. The biobanks that have participated in the survey come from the following autonomous communities: Aragón, Asturias, Balearic Islands, Basque Country, Cantabria, Castilla y León, Catalonia, Community of Madrid, Galicia, Murcia, Navarra and Valencian Community.
91.7% of the total number of biobanks that responded to the survey have managed samples for projects or created a collection of patients affected by Covid-19 in the course of the pandemic, and 75% have modified the procedure of obtaining IC, which involves its signature by the patient (or the legal representative) and the reporting staff.
Considering that the rest of the questions in the survey have focused on the modifications carried out in the way of managing IC, the results presented below correspond to a total of 27 biobanks. The remaining 25% did not answer any more questions in the survey.
It is especially striking that, among the 25% of the biobanks that did not modify the usual procedure for obtaining IC, there are several biobanks from hospitals in the Community of Madrid, the autonomous region most affected by the pandemic during the first of the two states of alarm.

Statistical analysis of the biobanks that were forced to modify the procedure for obtaining IC

One aspect that has been asked about has been the dates during which biobanks have been affected in obtaining the IC of Covid-19 patients, considering two different periods:

[20] https://biobancos.isciii.es/ListadoBiobancos.aspx (last visited 11/03/2021).

- First state of alarm caused by the Covid-19 disease (from March 14 to June 21, 2020). During this period, 17 of the 27 biobanks whose way of obtaining IC was affected did so from the week following the declaration of the state of alarm, which reflects the speed of action. This situation lasted until June 21 in 26 of the 27 biobanks.
- From the end of the first state of alarm to the start date of the survey. During this period, almost 90% of these 27 biobanks had their way of obtaining IC affected. This situation began on the same day as the end of the first state of alarm (June 22, 2020) for 75% of them. On the other hand, for 66% of biobanks, this situation lasted until the start date of the survey, that is, it was still in force at that time.

Regarding the Covid-19 patient samples managed by the biobanks, 25.9% of them have worked only with surplus healthcare samples, 11.1% have worked only with expressly collected samples, and the remaining 63% have worked with both types of sample.
In Figure 1, you can see how the management of IC has changed in biobanks for the case of patients diagnosed with Covid-19. These data are closely related to those obtained in question 12, which can be seen in Figure 2. The alternatives to the standard obtaining of the IC have been based mainly on allowing the exemption of its obtaining or the verbal consent.

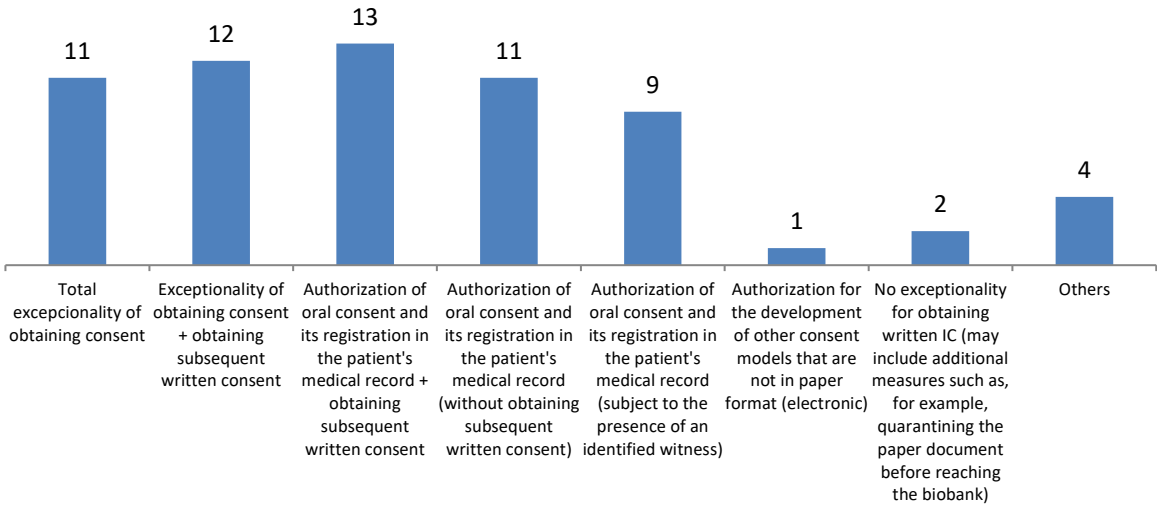


Figure 1. Measurement of the frequency in the application of several action choices regarding obtaining the IC of COVID-19 patients in Spanish biobanks (The same biobank may have applied more than one option)

ISSN 2284-4503

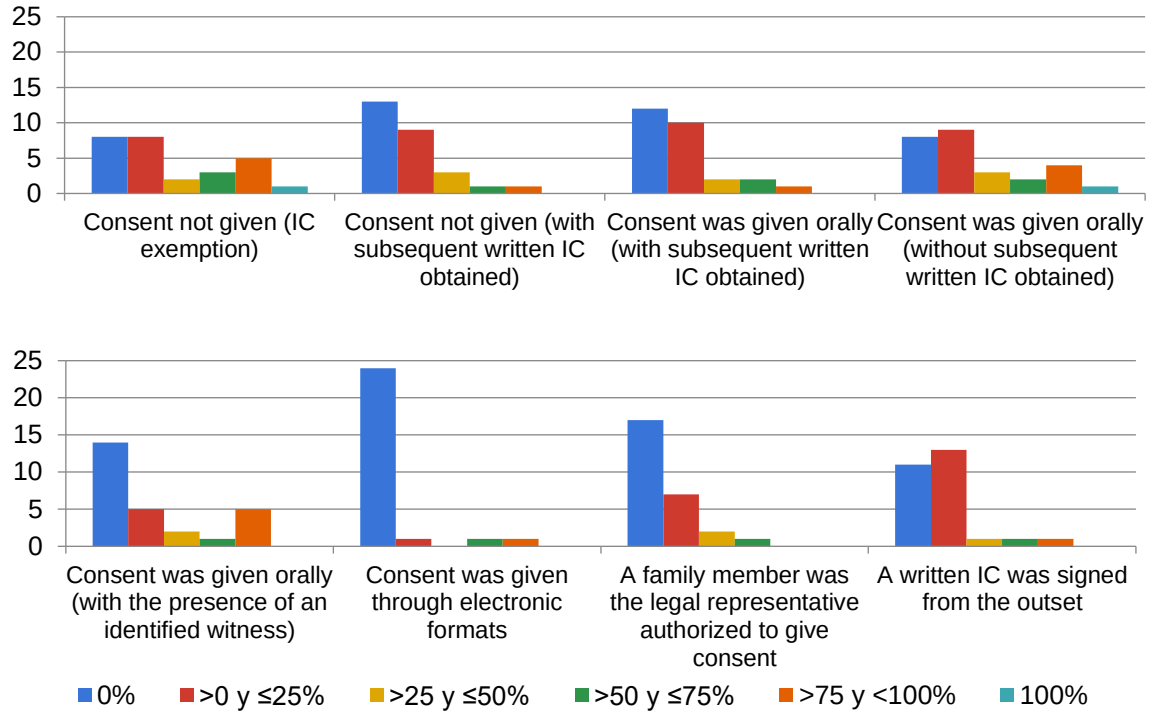


Figure 2. Estimation of the percentage of people who are in different situations related to IC with respect to the total number of people from whom a COVID-19 sample was obtained for biobank (The ordinate axis represents the number of biobanks that chose each percentage section as a response)

Regarding the people who did not sign the written IC from the outset, the process to collect that document in paper format is active in 44.4% of the biobanks (dated March 8, 2021), while in the rest is not active because it has not started (25.9%), has already finished (3.7%) or is not applicable (25.9%). In the cases in which the process is underway, the average percentage of people from whom the document has already been obtained is 45.7%.

For 51.9% of biobanks, the new way of IC management has undergone a modification again. Table 1 shows which have been both the most common previous and later options with respect to this modification. In this case, modification should be understood as the verdict of a REC. Therefore, the previous options are those allowed by the REC before the verdict, and the later options are those allowed by the REC after the verdict. It should be noted that neither the previous nor the later options contemplate obtaining IC through the usual procedure as the only possibility allowed.

	Previous option	Later option
Total exceptionality of obtaining consent	9	3
Exceptionality of obtaining consent + obtaining subsequent written consent	9	9
Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent	9	8
Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)	8	6

Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)	3	4
Authorization for the development of other consent models that are not in paper format (electronic)	1	2
Authorization of the consent given by the patient's relatives + subsequent consent of the patient	2	2
No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)	1	2
Others	1	0

Table 1. Number of biobanks whose RECs chose different choices in terms of obtaining the IC of COVID-19 patients as previous and/or later options regarding a change in the way of proceeding during the time in which the obtaining was not carried out by the usual method (14 biobanks have participated in these statistics)

Regarding the verdict of exceptionality, without being the options raised in question 8 mutually exclusive, 70.4% of the biobanks have affirmed that it was requested by themselves, while 22.2% recognized that it was requested by research groups of their center whose samples were prepared in the biobank. On the other hand, 29.6% of the biobanks admit that the verdict was issued by their REC without previous request.

These verdicts could have been motivated by the existence of other previous documents. Table 2 shows the influence of several reports or legislation on the verdicts of the RECs:

Autonomous (regional) legislation (decree, order ...)	6
Verdict/recommendation of a Reference Committee	8
AEPD (Spanish Agency for Data Protection) report on data processing in relation to COVID-19	8
Bioethics Committee of Spain report on the ethical-legal requirements in research with health data and biological samples in the framework of the COVID-19 pandemic	8
Document prepared by the Spanish Biobank Network "Management of obtaining ICs by the biobanks of the Spanish Biobank Network in the face of the pandemic for research on SARS-CoV-2 and the COVID-19 disease"	11
None of these options	6

Table 2. Measurement of the influence that the publication of different documents has had on the REC's verdicts of exceptionality (The numbers indicate how many biobank RECs relied on each document for the preparation of the verdict. Each biobank has been able to choose more than one option)

It should be noted that two of the responses that marked the option "None of these options" (Table 2) did so because the information for which it is asked was unknown in the biobank, referring to the REC to which they are assigned as responsible of the decision. In only 3.7% of the biobanks, the verdict of exceptionality was applied to all their active collections, while in 85.2% it was applied to the collections of patients affected by Covid-19. In addition, in 25.9% of the biobanks the verdict was applied to the Covid-19 patient samples prepared in the biobank and linked to research projects.

On the other hand, it should be noted that, in at least one in three centers, the verdict of exceptionality has not been applied equally to biobank samples than to samples linked to research projects on Covid-19 (however, it is necessary to indicate that half of the respondents do not know if it has been applied equally or not, so it is possible that the real data is much higher than that which

has been reviewed). Some of the differences that have been recorded in the survey in this regard are:

- "Total exceptionality of consent in research projects, although with anonymization obligation";
- "Absence of verdict for samples destined to projects";
- "Absence of written consent in the case of the biobank, and written consent signed by a witness in the case of the project";
- "Samples of non-Covid-19 patients collected with the usual consent".

4. Conclusions

Different conclusions can be drawn from the results obtained in the survey. First of all, it is evident that a large majority of Spanish biobanks have managed Covid-19 patient samples. Thus, it is clear that the activity of these research facilities has been altered by the pandemic, as has happened in all areas of the Spanish health system.

It has also been reflected in the results that this management of Covid-19 patient samples has caused an alteration in the usual way of obtaining IC in the case of most biobanks. Although this alteration was very frequent during the first state of alarm, it has continued to be present, albeit with a slightly lower frequency, in subsequent months. So much so that, in March 2021, approximately half of the biobanks that have managed Covid-19 patient samples (17 out of 33 biobanks) have not yet recovered the usual procedure for obtaining consent.

About 90% of the biobanks that have managed this type of sample have received surplus healthcare samples, which confirms that they have faced difficulties in obtaining IC through the usual course. The vast majority of RECs have made decisions so that biobanks could adapt to this situation. The most widespread response among RECs has been to allow exemption in obtaining consent or authorization of oral consent, subject, in both cases, to obtaining written consent at a future time when conditions are more favourable. For this reason, 70% of biobanks are currently collecting these documents or pending to start collecting them. On the contrary, the authorizations of electronic formats of consent or of relatives as legal representatives have been little-explored options.

It should be remembered that obtaining the IC in a future time under more favourable conditions is not compulsory when the use of the samples and data has been carried out in the framework of a public health emergency, as explained above. However, it can be a guideline made by a REC, which should not be understood as a legal obligation, but a moral one. Therefore, a refusal by the patient to consent to this retrospective use would not imply a legal problem, and it would even be possible to continue using said data if it is considered essential, usually on the condition that they are subjected to an anonymization process (or, in other words, an irreversible disassociation).

Notwithstanding the above, for half of the biobanks, the verdicts of the RECs for the transfer of samples from biobanks to research projects have undergone modifications during the course of the pandemic. In this sense, it should be noted that the total exceptionality of consent (that is, without the obligation to obtain it in the future) was an option that was frequently allowed at the beginning of the pandemic but that has no longer been allowed so assiduously in later months, perhaps because the health emergency (volume of work in hospitals, need for research samples) decreased

its level of severity. This is a clear indication of the fair balance that has been attempted to be maintained between the rights of the individual and the benefit of the collective.

In one out of every three cases, the verdict of exceptionality was issued by the REC by its own initiative. This means that, in most cases, it was the hospital's own biobank or research groups who asked the RECs for an exceptionality. It is worth highlighting the uniformity of action in those Autonomous Communities that have a Reference Ethics Committee or a single REC compared to those in which each center has its own.

Furthermore, the report that most influenced the verdicts of the RECs was the one prepared by the Spanish Biobank Network[3], which is a symptom of the importance of this Research Platform as a benchmark for the biobanks of the country. However, this document already included, at the time of its publication, the verdicts available from some RECs in relation to the management of Covid-19 patient samples by biobanks. Although only one Autonomous Community urgently published specific legislation, it can be said that it was the fastest and most effective action.

In general terms, the data show that the use of samples in research projects on Covid-19 has suffered more restrictions than the inclusion of this type of samples in biobanks. This circumstance is in line with Spanish legislation, which establishes that, while health authorities can carry out studies without IC of those affected in particularly serious situations, IC can only be dispensed with for secondary use of these data and samples by a research group when they have been pseudonymised and there is a favourable verdict of a REC[12].

It is also important to note that, in only one of the 27 biobanks, the verdict of exceptionality was applied for all types of active collections, in addition to the Covid-19 collection. This fact implies a high degree of compliance with the law, which indicates that written IC can only be dispensed with in cases of "general interest" or for public health reasons. In other words, the health emergency was not a sufficient reason for the exceptionality to become a generalized method. Thus, in most biobanks, the IC for sample types already collected before the onset of the pandemic continued to be obtained by the standard procedure. This is a significant fact of the legal and ethical rigor with which the RECs acted and that the exceptions to the general rule should be well justified.

ISSN 2284-4503

ANNEX

SURVEY ON INFORMED CONSENT (IC) MANAGEMENT DURING THE PANDEMIC

***Mandatory**

Biobank name (The biobank name is a field that will be kept confidential and is only collected to ensure that only one survey per biobank is answered)*:

Autonomous Community to which the biobank belongs*:

1. Has your biobank managed samples for projects or created any collections of patients affected by COVID-19 during the pandemic?*
   - ☐ Yes
   - ☐ No

2. Has the obtaining of IC been affected at any time and cannot be carried out by the usual procedure that involves signing it by the patient/legal representative and the reporting staff?*
   - ☐ Yes
   - ☐ No

(If you answer "No" in question 2, the survey ends and is sent. If you answer "Yes", you continue to answer the following questions)

3. Taking into account only the period that includes the initial state of alarm (from March 14 to June 21, 2020), could you indicate the dates between which obtaining the IC of COVID-19 patients has been affected? (Please answer this question only if applicable to you)

   From _____ to _____
   (Dates are chosen from a drop-down calendar)

4. Taking into account only the period from the end of the initial state of alarm (June 21, 2020) to the present, could you indicate the dates between which obtaining the IC of COVID-19 patients has been affected? (Please answer this question only if applicable to you)

   From _____ to _____
   (Dates are chosen from a drop-down calendar)

5. The COVID-19 patient samples managed by the biobank are (You can indicate more than one option)*:
   - ☐ Surplus of healthcare samples
   - ☐ Expressly collected samples

ISSN 2284-4503

6. In what terms has obtaining the IC of COVID-19 patients been affected? (You can indicate more than one option)*
   - ☐ Total exceptionality of obtaining consent
   - ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
   - ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
   - ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
   - ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
   - ☐ Authorization for the development of other consent models that are not in paper format (electronic)
   - ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
   - ☐ Others. Indicate: _____

7. Has the way of obtaining consent undergone changes during the time that it has not been carried out by the usual procedure?*
   - ☐ Yes
   - ☐ No

(If you answer "Yes" in question 7, you continue to answer what is asked in this same question. If you answer "No", you go directly to question 8)

Indicate from which previous option to which later option the biobank has switched to (You can indicate more than one option):

Previous options:

- ☐ Total exceptionality of obtaining consent
- ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
- ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
- ☐ Authorization for the development of other consent models that are not in paper format (electronic)
- ☐ Authorization of the consent given by the patient's relatives + consent of the subsequent patient
- ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
- ☐ Others. Indicate: _____

ISSN 2284-4503

Later options:

- ☐ Total exceptionality of obtaining consent
- ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
- ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
- ☐ Authorization for the development of other consent models that are not in paper format (electronic)
- ☐ Authorization of the consent given by the patient's relatives + consent of the subsequent patient
- ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
- ☐ Others. Indicate: _____

8. The verdict of exceptionality ... (You can indicate more than one option)*:
   - ☐ was requested from the biobank itself.
   - ☐ was requested by research groups of my center whose samples were prepared in the biobank
   - ☐ was issued by the Research Ethics Committee (REC) to which the biobank is attached, without previous request.

9. The verdict of exceptionality was supported… (You can indicate more than one option)*:
   - ☐ by the publication of autonomous (regional) legislation (decree, order...).
   - ☐ by a verdict/recommendation of a Reference Committee
   - ☐ by the AEPD (Spanish Agency for Data Protection) report on data processing in relation to COVID-19 (https://www.aepd.es/es/documento/2020-0017.pdf)
   - ☐ by the Bioethics Committee of Spain report on the ethical-legal requirements in research with health data and biological samples in the framework of the COVID-19 pandemic (http://assets.comitedebioetica.es/files/documentacion/Informe%20CBE%20investigacion%20COVID-19.pdf)
   - ☐ by the document prepared by the Spanish Biobank Network "Management of obtaining ICs by the biobanks of the Spanish Biobank Network in the face of the pandemic for research on SARS-CoV-2 and the COVID-19 disease" (https://redbiobancos.es/wp-content/uploads/DT-PS-0002-Informe-Gestion-Consentimiento-Informado-COVID-19.pdf)
   - ☐ It was not motivated by any of these options

10. The verdict of exceptionality was applied… (You can indicate more than one option)*:
    - ☐ to all the active collections of the biobank
    - ☐ to the biobank's COVID-19 patient collections
    - ☐ to COVID-19 patient samples prepared in biobank and linked to research projects
    - ☐ Others. Indicate: _____

11. Has the verdict of exceptionality in your center been applied equally to biobank samples as to samples linked to research projects on COVID-19?*
    - ☐ Yes
    - ☐ No
    - ☐ I don't know

    If not, could you explain the differences? _____

12. During the states of exceptionality adopted by your REC and up to the present time, taking into account the people from whom a COVID-19 sample was obtained for your biobank, what percentage of them do you think...* (Mark only one percentage for each question)

	0%	>0 and ≤25%	>25 and ≤50%	>50 and ≤75%	>75 and <100%	100%
…did not give their consent (IC exemption)?						
…did not give their consent (with obtaining subsequent written IC)?						
…gave their consent orally (with subsequent obtaining of written IC)?						
…gave their consent orally (without subsequent obtaining of written IC)?						
…gave their consent orally (with the presence of an identified witness)?						
…gave their consent through electronic formats?						
…had a relative who was the legal representative authorized to give consent?						
…signed a written IC from the outset?						

13. Regarding the people considered in the previous question who did not sign the written IC from the outset, is the process to collect their IC on paper active?*
    - ☐ Yes
    - ☐ No, it hasn't started
    - ☐ No, since it's already over
    - ☐ No, it does not apply to the particular case of my biobank

    If the answer is affirmative, indicate the approximate percentage of people from whom this document has already been obtained: _____

ISSN 2284-4503

ANEXO 9: Deliverable D1.2. Report on gender and age-related issues associated with the acquisition of informed consent

Horizon 2020 SwafS-17-2016

The ethics of informed consent in novel treatment including a gender perspective

Grant Agreement No:	741856
Project acronym:	I-Consent
Project title:	Improving the guidelines of informed consent, including vulnerable populations, under a gender perspective

Deliverable D1.2
Report on gender and age-related issues associated with the acquisition of informed consent.

Nature:[a]	R
Dissemination level :[b]	PU
Due date of delivery :	OCT-2017
Actual date of delivery :	
Document version :	v 0.1

Responsible partner & authors:	Jaime Fons-Martínez (FISABIO)
Cooperating partner & authors:	Javier Diez-Domingo (FISABIO) Fernando Calvo Rigual (FISABIO) Cristina Ferrer Albero (UCV) María Cubillo Diaz-Valdes (GSK)
Revision:	UNESCOBIOCHAIR, SPARKS&CO

[a] **R** = Report, **DEM** = Demonstrator, prototype, **DEC** = Websites, press & media actions, videos, **OTHER** = Software, technical diagram, etc

[b] **PU** = Public, **CO** = Confidential, restricted under conditions set out in Model Grant Agreement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 741856.

Document Information

Contract Number	741856	**Acronym**	I-Consent
Full title	Improving the guidelines of Informed Consent, including vulnerable populations, under a gender perspective		

Deliverable	**Number**	D1.2	**Name**	Report on gender and age-related issues associated with the acquisition of informed consent.
Task	**Number**	1.2	**Name**	Gender and age-related issues associated with the acquisition of informed consent.
Work package	**Number**	WP1	**Name**	Review and analysis
Date of delivery	**Contractual**	31/10/2017	**Actual**	30/10/2017
Nature	☑ R (Report) ☐ DEM (Demonstrator/Prototype) ☐ DEC (Websites, press & media actions, videos) ☐ OTHER (software, technical diagram)			
Dissemination Level	PU ☑ CO ☐			
Project Coordinator (contact person)	**FISABIO** Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana Avenida de Cataluña, 21. 46020 Valencia, Spain. Javier Diez-Domingo diez_jav@gva.es			
Project Officer	Zakaria BENAMEUR			

I-Consent Project Consortium

	P1	Fundacion Para el Fomento de la Investigacion Sanitaria y Biomedica Dela Comunitat Valenciana **FISABIO**	Spain
	P2	Ateneo Pontificio Regina Apostolorum **UNESCOBIOCHAIR**	Italy
	P3	Libera Universita Maria ss. Assunta di Roma **LUMSA**	Italy
	P4	Glaxosmithkline SA **GSK**	Spain
	P5	Synectika Research and Consulting LTD **SYNECTIKA**	United Kingdom
	P6	Sparks & Co **SPARKS&CO**	France
	P7	Meningitis Research Foundation **MRF**	United Kingdom
	P8	Ospedale Pediatrico Bambino Gesu **OPBG**	Italy

Revision History

Revision	Action	Date	List of changes	Author Responsible
V0.0		16/10/2017	None: first draft	

Table of contents

EXECUTIVE SUMMARY

Informed Consent process allows the subject to voluntarily decide his/her participation in a clinical trial. Generally, ICs are documents that are difficult to read, that do not include all stakeholders' perceptions and do not distinguish between subject's characteristics, (age, gender, demographic characteristics, etc.). This deliverable analyses the issues about gender and age.

MINORS

Research involving minors as subjects of research raises important questions regarding the participation of the child in the decision-making process.

Based on the fact that participation, understood as consent and/or assent in function of the legal relationship, is free and voluntary and is subject to a series of ethical and legal requirements, the decision making process becomes more sensitive due to the peculiarities of cognitive and moral development of the child.

Ethical and legal standards do not specify, in most cases, three of the key aspects in the decision-making process; information to be given to the child, how to assess the understanding of such information and how to assess the child's competence to make the decision.

The present systematic review of the literature has been oriented to find a response to these three key issues through a rigorous methodology in the search and treatment of information.

From the analysis of the information obtained we can observe that the exhaustiveness of the studies has not been high enough to be able to respond to each one of the aspects analyzed, with sufficient scientific evidence.

Regarding the information, we have been able to observe that in addition to being adapted to the age, the moral development of the minor and his emotional state must be individualized and continuous during the research study. There is no common pattern about the contents or the continent, as the range of situations surrounding each child may change in each case.

So, not only must we take care of what is said (quantity), but how it is said (method / format used), who says it (qualities of the person who reports), how often it says it (continuity and adaptation of information throughout the study) and what the minor wants to know or care about.

Giving information to the child without making sure he/she understood it would be tantamount to not giving any information. Therefore, it is necessary to check the understanding not only at the time of signing, but throughout the duration of the study. There is no method for evaluating validated understanding, since interviews and

questionnaires have been used with different structures and formats, without being able to reach a consensus. The studies that provide the most evidence use multimedia formats, on-line, images (comic) or video for presentation of information and evaluation of understanding, with positive results in some of them, especially in the section on risks. It is also observed that the lowest research subjects with health problems (cancer, HIV) tend to expect, by mistake, direct benefits of participation in research.

The comprehension of the information will be better if there is a good communicative relationship with the researcher and it is possible to discuss the information.

Understanding information and its integration by the child enhances the ability to make a coherent, free and autonomous decision. Determining this capacity is not an easy task, but four basic aspects must be evaluated: understanding of information, reasoning in the decision-making process, appreciation of the effects of participation and expression of a choice about participation.

At present, the reference tool is the MacCAT-CR that addresses these four blocks and has proven its validity and reproducibility. Although age cannot be a unique capacity requirement, it is the IQ that is the most influential variable. The scarcity of empirical data makes it necessary to carry out more studies with this tool. In the meantime, it is necessary to establish an effective relationship with the research team to determine the child's competence and ability to understand weigh risks and benefits and make a coherent and mature decision.

GENDER

This document goes over differences in communication by gender, taking into account all formats (verbal, non-verbal, writing and even using Internet). The methodology used has been a narrative review using different sources and databases such as Pubmed, Scopus, Web Of Science or Google Scholar; without limitation of date, but only considering documents written in English or Spanish.

The main paradigms in the study of gender differences in communications are presented, explaining the causes given to gender differences by each model, including the tendencies more extended nowadays, which highlight the importance of considering, by one side, gender as an activity that a person *does* rather than a characteristic that a person *has* and, by other side, the influence of other conditioning factors, apart from gender, in communication.

The findings in the field of gender differences in communication are frequently contradictory and the findings of one author are refuted by another. Even so, there are some differences that appear more often and most of them are related to the development of the role that society has assigned to men and women, so men usually have communicational behaviours

oriented to professional and public development, to transmit security, dominance, competitiveness, while women have communicational behaviours oriented to care, housekeeping and private development, looking tentative, caring and polite. These behaviours and stereotypes also influence the communicative behaviour in the relation physician-patient or in the use of social media and communication using ITCs. Even so several authors point out the existence of more similarities than differences between men and women; that the characteristics assigned to each gender style are not categorical and; that gendered styles are not assigned to one fixed gender and people can change from one to another depending on different situations (not all women must use the style typically assigned to them, and neither all the time, they can change from different styles, sometimes classically feminine and other times more archetypally masculine).

Accommodative behaviours have been associated with a positive evaluation of communication; in the field of relationship between physician and patient has been recommended to implement converge strategies, but cautiously and avoiding "overconverge" (for example to use "street language" during the clinical interview).

Most of the characteristics associated with female physicians have been evaluated by patients as positive and typical of a satisfactory experience. Usually physicians get more involved in communication with female patients.

There exist gender differences in the use of social media and in the eyetracking that should be taken into account when incorporating the use if ITCs to the IC process.

Most of the researchers found no significant differences in understanding of the IC form by gender, but the ones that found differences point out to a better comprehension by women.

Women indicate the characteristics that should have the professional who supplies information about the study: has to have knowledge of the study, appears secure and be able to answer the questions about the research; be accessible and available to give guide to the woman about the research; should have an attentive and accessible attitude, avoiding seeming arrogant. They prefer to receive the information in groups of women and individually (both complementary); and in written and orally format (also complementary). The conversation with the physician is very important and valued. To been able to decide about participating or not they should have information about risks and benefits, efficacy and possible side effects and inconveniences (short, medium and long term ones). They give more importance to the manner the information is provided (clearly and objectively to be easy understanding) than to the quantity, but too much information could be counterproductive. Use of audio-visuals contribute to improve the retention of the information and to assure that same information is provided to all potential participants.

TABLE OF MAIN RESULTS

Number	Short Description	Reference page
1	Gender is one of the conditioning of communication activities, but there are others that must be taken into account (biophysico-psychological, environmental, cultural patterns, socioeconomic-educational levels, shared behaviours)	20
2	Gender differences in communication are a controversial topic. Often, findings of one author's are refuted by others. Some researches point out that there are more similarities than differences between men and women. The differences are not categorical.	29
3	Some researchers point out that there aren't significant differences in understanding of the Informed Consent (IC) by gender. Others indicate that women have better comprehension.	50-51
4	There exist gender differences in the use if ITCs and in eyetracking	53-60
5	The communication physician-patient also presents differences by gender; most of them coincide with gender differences in non-clinical environments. Characteristics attributed to female physicians have been identified as more positive and satisfactory.	62-64
6	The oral explanation of the IC is a key factor for its understanding. Women prefer the IC to be presented in group and individually (complementary) and orally and writing (complementary).	62,70-71
7	Bento et al. studied the women's opinion about the IC process	69-72
8	To improve the understanding of IC is important to tailor it to the patient's characteristics	72
9	There are few scientific articles with high quality of evidence that help determine the information necessary for the consent of a child to participate in research	101
10	Assent must include at least: reason why is asked to participate; description of procedures; how might experience them; right to revoke participation at any time; decision of the child is free and voluntary; confidentiality	102, 103
11	It is recommended to individualize the information provided to the child, based on their age, emotional state, health status and what they want to know. Adapt the extension (short), language (simple without technicalities), format (multimedia).	103, 104
12	It is necessary to establish a good communication relationship between the minor, his / her parents and the research team	104
13	There are articles in the scientific literature that evaluate the understanding of assent information for research in minors, but without a consensus on the tool to be used. The use of questionnaires is common, but they are very heterogeneous.	105-109
14	It is difficult to determine the competence of a minor to participate in a process of assent in clinical research. The only tool validated today is the MacCAT-CR, but there are experts who value more discussion with the child and their parents to determine it.	109-113

TASK DESCRIPTION

Gender and age are two major factors to consider in the review of scientific literature in the field of IC. Identifying their different characteristics and needs is very important for proper development of the guidelines.

Because of the differences between both subjects (age and gender), this document is divided in two different parts, the first part is dedicated to gender adaptation, and concretely, gender differences in communication and its application to the IC; the second part is dedicated to the age, and specifically the topic of informed consent by minors (assent). Although they are part of the same deliverable, each part has its own introduction, methodology, results, conclusions, bibliography, etc.

In the case of age issues, the focus on minors is justified because it is a highly identifiable group with characteristics common to all of them, and also because they are considered as a vulnerable population and with legal differences compared with other age groups. Other age groups, such as elderly people, were considered, but sonly specific disease problems more common in that age range (such as dementia) were considered might affect the informed consent process, but not characteristics of the age group itself, they were discarded.

In the case of gender issues, it has been considered that the contents the IC should include doesn't differ essentially by the gender of the participant, unless some special cases as during pregnancy or breastfeeding, but these are included in the soft and hard law. Because of that, the differences analysed in this document are concerning to the style of communication, because they should be taken into account during the elaboration of the IC forms and the rest of the IC process.

The review about the informed consent by minors (assent) has been done using a systematic review while the review about gender differences in communication has been a narrative review.

A. GENDER ISSUES ASSOCIATED WITH THE ACQUISITION OF INFORMED CONSENT: GENDER DIFERENCES IN COMMUNICATION.

A.1. INTRODUCTION

Gender is one of the main factors to consider in the field of the Informed Consent (IC) process. The contents that the IC should include don't differ essentially depending on the gender of the subject, but only special cases during pregnancy and breastfeeding are remarkable. There are differences by gender that must be taken into account to improve the IC process and its understanding, ensuring his/her autonomy in the decision taking about participating or not in the research, and as the H2020 says to *"integrate the needs and behaviours of women as well as men in research content"* [(1)].

The objective of this document is to analyse and explain the differences in communication by gender to be able to adapt the IC.

Which gender differences are considered?

The document includes differences about the patterns of communication, use of language, social media and Internet.

The document is not focused on the representation of women and men in different fields as publicity, cinema/TV, literature or linguistic. Neither on the use of non-sexist language, that is a very important aspect that must always be taken into account, as we will do in the entire project, but its analysis is not an objective of this document.

What contents can be found in the document?

In this document the differences following this index are analysed and explained:

1. Introduction
2. Sex VS Gender
3. Theoretical bases to the differences in the pattern of communication by gender:

- Introduction
- Main paradigms
- Linguistic style accommodation

4. Differences in the patters of communication by gender:

- Motivation to communicate
- Main characteristics of the different styles of communication

5. Gender differences in skills

- Gender differences in scholars: the PISA survey
- Gender differences in adults: the Survey of Adults Skills (PIAAC)
- Differences in gender comprehension of IC by gender

6. Online Gender Differences

- Gender differences in online communication
- Gender differences in online shopping
- Gender differences in social networking sites
- Gender differences in smartphone and texting
- Gender differences in eye tracking

7. The patient - physician communication

- Why is important?
- Gender differences in the relationship physician-patient

8. Women's opinions about the informed consent process
9. Conclusions
10. Recommendations for the gender approach in IC
11. Bibliography

What methodology has been used?

The information included in this document is the result of the analysis of papers and books founded in a narrative research done in different databases (Scopus, Pubmed, Web Of Knowledge, Scholar Google and Dialnet) and in guidelines and organisation webpages. The studies included are from the field currently known as studies of Language, Gender and Sexuality[c, (2)].

Important remarks:

There are two important ideas that Cameron [(3)] says that we want to remark, because they are important to understand our point of view of the gender-related differences shown in this document:

1. The differences are not categorical and are based on the results of different studies that have found statistically significant differences between male and female trends or patterns.
2. The differences among each gender (age, socioeconomic status, ethnic and geographical origins, religious beliefs, etc.) must be taken into account, because they

[c] This field includes the studies about the differences in communication between men and women.

influence on the behaviour and produces a variety of masculine and feminine styles in different contexts. These differences can be wider than those produced by gender.[d]

[d] This is one of the main ideas of the diversity paradigm that is explained in the section 3.1 of this document.

A.2. SEX VS GENDER

Sex and gender are two different concepts that have sometimes been used, wrongly, as synonymous. The Guidance on Gender Equality in Horizon 2020 [4] defines them as follows:

- **Sex** refers to "*biological qualities characteristic of women and men, boys and girls, in terms of reproductive organs and functions based on chromosomal complement and physiology. As such, sex is globally understood as the classification of living things as male and female, and intersexed.*"
- **Gender** is a *"socio-cultural process. It refers to cultural values and social attitudes that together shape and sanction "feminine" and "masculine" behaviours, and also affect products, technologies, environments, and knowledge."*

  The European Institute for Gender Equality (EIGE) [5] gives a more extended definition of gender and indicates that gender *"refers to the social attributes and opportunities associated with being female and male and to the relationships between women and men and girls and boys, as well as to the relations between women and those between men. These attributes, opportunities and relationships are socially constructed and are learned through socialisation processes. They are context- and time-specific, and changeable. Gender determines what is expected, allowed and valued in a women or a man in a given context. In most societies, there are differences and inequalities between women and men in responsibilities assigned, activities undertaken, access to and control over resources, as well as decision-making opportunities. Gender is part of the broader sociocultural context. Other important criteria for sociocultural analysis include class, race, poverty level, ethnic group and age."*

Following the descriptions given above sex and gender differences have different contexts, referring sex to the biological and physiological characteristics and gender by the sociocultural context and the relations of power.

García, Jiménez and Martínez [6] highlight the following characteristics of the concept of gender saying that is:

- **Relational:** It doesn't refer to women or men in isolation; it refers to the relationships that are built socially between one and another.
- **Asymmetrical / hierarchical:** Differences between women and men aren't neutral; society gives more importance and value to the characteristics and activities associated with masculine gender and produce unequal power relations.
- **Changing:** Roles and relationships are modified over time and place, being susceptible to changes by interventions.
- **Contextual:** Gender relations are different depending on other characteristics, such as ethnicity, class, culture, etc.

- **Institutionally structured:** It refers not only to relations between women and men on a personal and private level, but also to a social system based on institutional values, legislation, religion, etc.

In this document the analysis is focused on gender issues, making reference to the ones that have its origins in the social aspects, not in the biological or physiological ones.

A.3. THEORETICAL BASES TO THE DIFFERENCES IN THE PATTERN OF COMMUNICATION BY GENDER:

A.3.1 INTRODUCTION

The relationship between communication and gender has been a topic that has aroused interest since long time ago[e], but it wasn't until the 1960's when the number of researches on this topic experimented a continuous increase. (7) In 1975 the relationship between gender and communication emerged as a differentiated investigation topic and from 1990's the increment of the studies in this field has been exponential. [8]

One of the effects of the rise of the studies about this topic has been the development of its own terminology, being especially important the creation of the term "*genderlect*" that is defined by the Encyclopedia of Language and Linguistics as "*A type of language usage that is prototypically associated with speakers of one gender*" [9]. The concept, which appears for the first time in the gender oriented sociolinguistic literature of the 1970s, [10] has its origin on 1953 when Weinrich said that sex could be a relevant variable in language contact situations; [11] [12] and in its traditional meaning contrast the male and female speech as two clearly different and stable gendered varieties. [10] Authors like Glück, quoted by Motschenbacher, consider this term more appropriate than "*women's/men's language*". [10]

During the last years, and particularly with the rise of the diversity paradigm, this concept has been widely criticised because of its dichotomy, and several researchers have wondered if it still being useful. Some authors refuse the term because they consider that to use it legitimates the masculine domination [13] while others express that is inadequate to continue using the traditional approach to gendered variation, because it doesn't reflect the actual use of language done by men and women, but they still find the term 'genderlect' useful and suggest to redefine it. In this same way Motschenbacher [10] indicates that "*the term 'genderlect' does not have to be dismissed entirely. It can be used in the knowledge that it plays a significant role in the performative construction of gender. This does not mean that all women and men use a female or male genderlect respectively. People have a multitude of speech styles at their disposal which they use depending on context",* and propose to redefine the term genderlect in a postmodern way *"as standing for a linguistic style that performatively stages gendered language stereotypes".* [10]

Tusón (14) doesn't use the term genderlect, she talks about different styles (the feminine style and masculine style) and, in the same direction that Motschenbacher, suggest the existence of two different discursive styles, and calling them feminine and masculine style

[e] Otto Jespersen in his book Language: Its Nature and Development (1922) identify the first mentions to the differences in 1664, he indicated that "the first to mention their distinct sex dialects was the Dominican Breton, who, in his Dictionnaire Caraïbe-français (1664), says that the Caribbean chief had exterminated all the natives except the women, who had retained part of their ancient language."

doesn't mean that all men must use all the typical traits of the masculine style, neither should all women the feminine style because these styles are just trends. She also points out that due to the characteristics of some men and women identity or different situations can use the traits usually assigned to the other sexual group.

Returning to the discussion on the appropriateness of using the term genderlect, Castellanos (15) argues that the term genderlect can still be useful because it brings us closer to understanding how the feminine and masculine identities are constructed. She defines genderlects as *"the differences of style between the feminine and masculine discourse, culturally conceived"*, so she highlights that the genderlects *"are not ascribable to men or women as biologically determined groups, but correspond to the cultural characterization of what types of expressions and attitudes are considered feminine or masculine in a specific sociocultural context, and therefore what types of behaviour are expected of men or women"*.

Poyatos indicates that gender is recognized as a conditioning of communication activities, but it is not the only one. He identifies the following conditioning factors of communicative activities: biophysico-psychological (such as ethnic group; gender; age; physiological, medical and emotional state; nutritional habits; psychological configuration); environmental (natural, modified, built and objectual environment; socioeconomic and educational background); cultural patterns (general cultural style; regional or subcultural groups; religious and moral values; relationships and role expectations; norms of etiquette and good manners; aesthetic values); socioeconomic-educational levels (from lowest socioeducational status to hyperrefined) and; shared behaviours (family and conjugal borrowings; borrowing from social models; social and occupational groups. [16] It is important to take into account the influence all of them have on communication activities.

Poyatos [17] also specifies that discourse has a basic triple structure: "what we say" (verbal language: the words); "How we say it" (paralanguage[f]); "How we move it" (kinesics[g]).

Independently of its format, the Informed Consent is a communicative act so it is important to analyse and understand the differences of communication by gender in order to adapt messages to each audience because, as Motschenbacher indicates, *"genderlects, therefore, provide resources for gendered identity performances which can be exploited strategically (for instance in advertising) or used as a form of ritualised practice (in people's everyday communities)"* [10], and if fields such as advertising consider genderlects important probably it will be convenient to take it into account to make the messages more understandable and to bring people closer to medical research.

---

[f] The Encyclopedia of Language and Linguistics defines Paralanguage as: "Relatively nonsystematic variations of tone of voice, e.g., nasalization or breathy voice used to a particular effect; sometimes also nonvocal phenomena such as eye movements, facial expressions, etc." *(9)*

[g] The Encyclopedia of Language and Linguistics defines Kinesics as: "The study of the use of gesture, facial expression, and bodily movement as meaningful elements in a system of communication." *(9)*

A.3.2 MAIN PARADIGMS

Historically there have been different explanations to the gender differences that are represented in 4 main paradigms: the deficit model; the dominance approach; the difference theory; and a group formed by diversity, constructivist and performative approaches, which are more extended nowadays and are presented in this document all together because, independently of the denomination of each one, they have a lot of common points and we consider that it is the best for the purpose of this document.

A.3.2.1 The deficit model

The deficit model identifies women´s language as inferior to that of men, which is considered as the norm.

The linguistic Otto Jespersen did the first academic study on the differences between male and female language in 1922, in his book titled *Language: Its Nature and Development* (18), he analysed linguistic gender differences on several topics such as taboos, phonetics and grammar, vocabulary, choice of words, use of adverbs, frequency leaving exclamatory sentences half-finished or grade of formality. He suggested that there were two separate languages or dialects and he described women's speech as deficient compared to that of men, which was considered as the norm. [(12)] Jespersen's theories have been very criticised by the feminist authors who consider them sexists, paternalists and self-flattering. [(19)]

Another main representative of the deficit model is Robin Lakoff [(20)], who uses the term *"women's language"* to reflect the double discrimination that women suffer with language: on the one hand the discrimination in the way women are taught to use the language (*talking like a lady*) and, on the other hand, the way the use of language treats women (*talking about women*). She indicates that both discriminations want to relegate women to some subservient functions and treat her as a non-serious person. She compared the lexicon and syntax of women's and men's speech[h], concluding that women's speech characteristics made it weak with an ineffective style and inferior compared to men's speech (the norm). Cameron [(3)] identifies the following characteristics of women's speech in Lakoff's work:

a) Preference for milder over more strongly tabooed expletives.
b) Exaggerated politeness.
c) Elaborate colour vocabulary.
d) Use of empty adjectives ('lovely,' 'divine').
e) Use of intensifiers ('so nice').
f) Hedging to reduce the force of an utterance and/or the speaker's degree of commitment to it.

h Because of its objectives, this document focuses only in the first aspect of the "women's language" that identifies Lakoff ("talking like a lady").

g) Phrasing statements as questions, using rising intonation and/or end-of-sentence question tags.

Lakoff explains that many of these characteristics of the women's speech reflect insecurity and are produced by the male-dominated sexist society. [3] In relation with this Hidalgo [12] indicates that the *"deficit model"*, with the characteristics attributed to the *"women's language"*, emphasises the idea of female speakers' lack of confidence that is shown through "*hesitations, tag questions, rising intonation in declarative sentences, and epistemic modal markers."*

Uchida indicates that Lakoff's theories have been criticised, some critics questioned her methodology (based on unsystematic observations and intuition); others tested her hypotheses of *"women's speech"* getting contradicting results; and her concept of *"women's language*" has also been seen as confounding social status with sex. Even so she highlights Lakoff's contribution as *"one of the first and most influential works stating that it was inequality between the sexes in society that was reflected in language use, rather than the genetic inferiority of women"* [21].

A.3.2.2 Dominance approach

The dominance approach explains the differences between the language of women and men as a reflection of social differences and power.

As Cameron says "*any difference in men's and women's ways of communicating is not natural and inevitable, but cultural and political*" [22].

This paradigm was constructed on the basis of the deficit model and especially from Lakoff's contribution; it rejects the linguistic superiority of men and explains the differences with the fewer assertive attitude of women as a result of the denial of their access to language of power. [12] Fishman, quoted by Maltz and Borker, point out that the norms of behaviour ensure the maintenance of power and interactional control by men. [23]

Zimmerman and West [24] indicate that men exercise in the conversational relations with women the same dominance and power that they exercise in other areas. This asymmetry of sex roles is reflected in different patterns of behaviour during conversational interventions between men and women (cross-sex conversations), as in the interruptions, silences or the support for partner developing topics.

Brown [25] studied, in a Mayan community, the relationship between communicative strategies and social status and how it was reflected in the politeness (more widespread among women), and she indicated that as a higher level of politeness is expected from inferiors to superiors, is predictable that women speak in a more formal and polite way, because of their secondary status relative to men. Cameron reaffirms the idea of the influence that gender power relations have on the linguistic by stating that *"men are 'less*

polite' not because they cannot use these strategies, but because in most situations they feel no need to" [26].

Fishman [27], in her analyses of gender's hierarchy in everyday interaction, realised that there were gender differences in the distribution of work in the conversations. Women tend to work more in the conversations and take a more active role insuring interaction than men (for example, asking more questions, using attention beginnings, doing support work when men are talking or doing active maintenance and continuation work in conversations); men are more likely to discourage interactions started by women than vice versa. She also realised that even women tend to work more in the conversations they usually have less successfully than men starting conversations or introducing topics; the explanation she gives to this effect is that men success because women do an effort in response to their attempts, while women fail because of the lack of men's capacity to do the interactional work. She points out that there is a "*division of labour in conversation*", where women are the "*shitworkers*" that do the routine work and men are who control the process and get the benefit.

Other authors (as Bilious and Krauss; Herring, Johnson, and DiBenedetto; or Kollock, Blumstein, and Schwartz) show how different aspects in the communication reflect the hierarchical social differences by gender, as interruptions and overlaps; control of the turn taking and duration; topic selection; silences; or use of backchannels. [12]

A.3.2.3 Difference theory

The difference theory considers that gender differences in the communication are caused because men and women belong to two different subcultures, with different values, and this is reflected in the conversation.

This paradigm defends that men and women belong to two different subcultures and that affects to their communication behaviours,[12] but even they have different rules of conversation and styles, both are equally valid. [21] Gray refers it very well with the title of his book *Men are from Mars, women are from Venus* [28] that suggests that the differences between them are so wide as if they came from different planets [29]; without going so far, Maltz and Borker [23] equate the difficulties in the communication between genders with the cross-ethnic communication. Mulac [30] indicates that the difference is in the way they use the language, not in the language they use, saying that *"There are two abiding truths on which the general public and research scholars find themselves in uneasy agreement: (a) Men and women speak the same language, and (b) men and women speak that language differently".*

Tannen indicates that the origin of the differences is the education that boys and girls get during the childhood, she says that *"even if they grow up in the same neighborhood, on the same block, or in the same house, girls and boys grow up in different worlds of words. Others talk to them differently and expect and accept different ways of talking from them. Most important, children learn how to talk, how to have conversations, not only from their parents but from their peers"* [31], she also emphasizes the importance of the games boys and girls play, and indicates

that the objectives, strategies and values of each kind of game makes them to acquire different gender appropriate behaviour. [32] And points out that these cross-cultural communication differences produce frictions between men and women. [31]

Maltz and Borker defend that rules of interacting in different situations are learned approximately at the age of 5 to 15 from peers of their own sex (that are with the ones that socially primarily interact). [23] They also emphasize that the fact that boys and girls learn to use different genderlects, give them different rules and patterns of use and understanding of communication that produce the miscommunication between genders. [33]

Alami, in her analyses of Tanen's work, underlines that men and women speak different because they try to accomplish different things when they talk, and says that: *"Men approach conversation as a contest. Thus, they prefer to lead a conversation in a direction in which they can take central role by for example telling a joke, displaying information or skill, which Tannen calls "report talk" (public speaking). While most women's conversation is a way of establishing community and creating connection, which she calls "rapport talk" (private speaking)"* (33).

Mulac, Bradac and Gibbons [34] consider that the *dominance approach* and the *difference theory* aren't exclusive and that each approach underlines different parts of a unitary process. This idea, which differs from the general tendency of considering both paradigms as contraries, has also been put into practice by other authors as Bogaers who combines both models in her research about gender differences in job interviews. [35]

Many authors critiqued the difference theory; Talbot shows the different critics that authors have done to this approach, pointing that *"the foremost concerns are the erasure of power and a tendency to overgeneralize, brought about by disregard for contextual considerations other than gender"* [32]. And she highlights that Thorne considers exaggerated the sex segregation in childhood; and Cameron points that the affirmations about the miscommunication between adults ignore issues of conflict over rights and obligations in times of social change. [32] Uchida also criticises this approach because on the one hand she considers the idea of the different "cultures" too simplistic to account for all that happens in mixed-sex conversation; and on the other hand she considers inappropriate the dichotomization of "power" and "culture" as independent concepts because all social interaction occurs in the context of a patriarchal society. [21]

A.3.2.4 Diversity, constructivist and performative approaches

Diversity, constructivist and performative approaches highlights the importance of considering, by one side, the gender as an activity that a person *does* rather than a characteristic that a person *has* and, by other side, other conditioning factors, apart from gender, in the communication.

Diversity, constructivist and performative approaches are nowadays the prevalent perspectives in the studies of Language, Gender and Sexuality; they break with the dichotomy between men's and women's language and with the assumption that all men and all women have the same linguistic behaviour, considering that old approaches reproduce gender stereotypes. [2] [3] [12]

Acuña [2] shows that the starting point of these paradigms is that societies and cultures establish predominant models of "*femininity*" and "*masculinity*" as signs of identity for women and men respectively; and the individuals can behave following this gender patterns or transforming (and challenging them) in a greater or lesser extent. Motschenbacher [10] identify that there are "*hegemonic and non-hegemonic gender styles*", indicating that both of them are possible. The *hegemonic* are the ones that are stereotypically associated with femininity and masculinity in a culture; the non-hegemonic are subversives, as they deviate from what are considered coherent gender styles; and they only have significance in comparison to mainstream practices, because what is considered subversive in one context may be considered non-subversive in another, and vice versa. [10]

Butler [36] understands gender as "*performative*", as *"not something a person 'has' but something a person does"*, so gender identity is a fluid construct rather than a natural given. Motschenbacher [10], following this *performative* approach, emphasises his rejection to the idea that people speak a genderlect because of their demographic gender. In line with this approach, Acuña [2] considers that is important to speak of *"masculinities"* and *"feminities"* reflecting the multiple forms of feminine and masculine identities. Cameron [37] indicates that Butler's performative concept of gender made researchers' attention to focus on the range of ways the resources of linguistic variation could be used to perform gender.

The *diversity* paradigm considers men and women as heterogeneous groups, with internal differences among them, that can be even bigger than the ones between genders [3] [12]. As Cameron [3] says *"people are after all never just men and women, but are always men and women of particular ages, classes, ethnic and geographical origins, occupations, social roles and statuses, and religious and political beliefs. The form gendered behaviour takes is inflected by these other dimensions of identity and experience"*. She also emphasizes that linguistic variability can be used to produce a range of masculine and feminine styles adapted to different communities or contexts.

Motschenbacher [10] identifies as a problem to consider gender as the only and independent conditioner for language variation and indicates that it interacts with other parameters as race, age, class or context; and indicates that if we find differences between male and female linguistic behaviour it doesn't mean that gender is the main and only factor that causes that difference. He proposes to focus on intra-gender diversity instead of the inter-gender difference and says that it will allow understanding that the linguistic behaviours of women and men have more similarities than differences. Poyatos [16] also remarks the importance of

different conditioning of the communication activities and identifies them (see Figure 1 in the section 3.1).

Acuña [2] indicates that the adoption of this approach implies a change in the objectives of the researches, from exploring the differences in the ways of speaking and communicating by men's and women's, to analyse how communicative practices construct different versions of masculinity and femininity and which are the discursive resources involved in these processes and in which contexts acquire relevance. Cameron reflects it very well when she says *"In a gender difference framework, the fundamental question is, 'how are women different from men?' In a diversity framework, that question will immediately be met with another question: 'which women and which men do you mean?'"* [37].

A.3.3 LINGUISTIC STYLE ACCOMMODATION

Once explained the main paradigms to explain the reasons of gender differences in communication, is important to know the strategies that individuals use to adapt their communication depending on the characteristics of his/her communication partners, with a special focus on the gender. For this purposes in this document is briefly explained the *"Communication Accommodation Theory" (CAT)*[i]. Watson and Gallois [38] point out that one of the differences between this theoretical model to others of communication is that it takes the social identity, the personal identity or both into account that may drive the speech's partner motivation in a conversation.

Bylund, Peterson and Cameron explain that the CAT *"focuses on the ways individuals modify their communicative behavior as a result of their communication with each other (…) explains how behavioral strategies (e.g., rate of speech, eye contact, gestures) are utilized to accommodate speech and nonverbal behavior"* [39]. Namy, Nygaard and Sauerteig indicate that people use accommodation to achieve particular social goals, as for example social approval or acceptance, attraction, affirmation of identity (group or individual), and the facilitation or regulation of discourse; to been able to accommodate is necessary to monitor the indexed characteristics of their interlocutors and adapt the own characteristics to them. [40]

The CAT came up from the Speech Accommodation Theory (SAT) indicating how the accommodation not only involves the speech (as verbal language) but also includes the paralanguage, the kinesics and the different communication media (as speech, email or writing). [41] The origins of the SAT were in the early 1970s with the aim of understanding the shifts in the speech styles, with a special focus on accents and dialects; in the 1980s

[i] CAT is just one of the several interpersonal communication theories that exist and it has been selected by the authors of the document because of its utility for this topic. For a brief overview of other useful interpersonal communication theories we recommend to read the article "A practitionert's guide to interpersonal communication theory: An overview and exploration of selected theories" written by Bylund, Peterson and Cameron [39]

researchers used this theory in several contexts to examine how different social groups (basically focusing on the age and ethnicity/culture) use and perceive accommodation, by this time the theory was being re-named or re-conceptualized as the CAT (as said above). Since then the CAT has been developed and applied to different contexts, resulting in a useful theory to study the dynamics of interactions by examining the association between accommodative behaviours and different relational and identity outcomes and which can be applied to both interpersonal and intergroup interactions. [42]

CAT proposes 3 different processes or approximation strategies that Soliz and Giles describe as follows: [42]

1. Convergence: *"a strategy whereby individuals adapt their communicative behaviors in such a way as to become more similar to their interlocutor's behavior. Typically, this is done to seek approval, affiliation, and/or interpersonal similarity as a manner of reducing social distance."*
2. Divergence: *"leads to an accentuation of speech and nonverbal differences between the self and the other. Often (but not always) the motive behind divergence is precisely the desire to emphasize distinctiveness from one's interlocutor, expressively highlighting contrasting group identities."*
3. Maintenance: *"where a person persists in his or her original style, perhaps for reasons of authenticity or consistency, regardless of the communicative behavior of the interlocutor."*

Muir, Joinshin, Cotterill and Dewdney [43] point out that accommodative behaviour has been associated with a positive evaluation of the communication, the individual, and the relationship, while nonaccommodation has been with negative evaluations. They indicate that:

- Convergence in speech or nonverbal behaviours facilitates the perception of similarity among interactants.
- Greater similarities in attitudes and personality are perceived when dyadic participants converged in pause duration.
- Convergence in nonverbal behaviours (as mimicking body language, facial expressions, or gaze) has been related with feelings of rapport among interactants.
- Verbal mimicry increases the perception of the speaker's attractiveness.

Even the studies of Language, Gender and Sexuality only represents a small percentage of all the CAT-based research done (around 13,5% of them until December 2010) [42], there exist several researches that have studied the accommodation theory to gender-preferential language in different contexts (some of them as specifics as in e-mails [44], graffiti from toilets [45] or a medical visit).

Some authors indicate that the accommodation may be limited only to female speakers, who consciously or unconsciously accommodate their style when are with a male partner, while

others defends that both genders converges and even they do it in the same proportion. [46] Other authors show how gender-preferential style are more present in same-sex conversations than in mixed-sex conversations; and this can be explain by the accommodation (convergence) than men and women do to the gendered style of their partner in mixed-sex conversations. Accommodation in same-sex conversation also exist and is erroneous to assume that the style used in a same-sex conversation is the "natural" one; in fact, as boys and girls usually spend more time in same-sex groups, they are more used to accommodate to the gender-preferential style of their own group, and they are also more motivated to do it to accentuate the similarities with the in-group members. [44] Other authors point out that, in mixed-sex conversations, men and women diverge from each other in their speech behaviours to stay consistent with traditional sex role stereotypes. [43]

An example of the accommodation studies are the ones that found gender differences in vocal accommodation, indicating that women are more likely to accommodate than men, Namy, Nygaard and Sauerteig found this differences robust and they suggest that are due to gender differences in the perception of indexical information (either because of a better perceptual sensitivity or because they pay more attention). [40]

A.4. DIFFERENCES IN THE PATTERS OF COMMUNICATION BY GENDER

Turabian, Minier-Rodriguez, Moreno-Ruiz et al. [47] indicate that gender differences in communication is a controversial topic, because some authors identify significant differences will others refuse them and say that there aren't differences. Even so, in the last decades the number of researches about differences between women and men behaviour have increase and there is an extended perception that there exist differences in the way men and women communicate and in the motivations to do it. Griffin highlights that after a long systematic research he found at least three cautions: [48]

1. There are more similarities than differences among men and women.
2. Greater variability of communication style exists among women and among men than between both groups.
3. Sex is a fact; gender is an idea.

This chapter contains a compilation of the differences between male and female trends or patterns found in several articles and books published but, as Cameron says, they are not categorical. [3] Another important idea is that, as Wallentin says, *"researchers bring their own preconceptions, or gender stereotypes, with them in their interpretation of data"* [49] so is recommended to be cautious with the results.

A.4.1 MOTIVATION TO COMMUNICATE

Tannen points out that men and women have different motivations and needs to talk that influence the style of their speech. She indicates that *"more men feel comfortable doing "public speaking," while more women feel comfortable doing "private" speaking"* [31]. In fact, she indicates that men are talkative in public and silent in private, whether women are silent in public and talkative in private, showing that men speak more than women in public arena and women more than men in private conversations. [31] [50]

Holmes indicates that most women enjoy talking and consider it important to keep in touch, so they use language to establish, nurture and develop personal relationships. While men understand language as a tool to obtain and transmit information; seeing the conversation as a means to an end. [51]

In the same way, several authors point out that men are motivated to negotiate, maintain status, assert dominance, preserve their independence and to achieve utilitarian goals, while women use language as a way to form and maintain connection with others and negotiate relationships. [31] [33] [50] [52] As Griffin says *"girls learn to involve others in conversations, while boys learn to use communication to assert their own ideas and draw attention to themselves"* [50].

Maltz and Borker identify the 3 major things done by boys and girls with speech: [23]

- Girls:

1. Create and maintain relationships of closeness and equality.
2. Criticize others in acceptable ways
3. Interpret accurately the speech of other girls.

- Boys:

1. Assert one's position of dominance.
2. Attract and maintain an audience.
3. Assert oneself when other speakers have the floor.

A.4.2 MAIN CHARACTERISTICS OF THE DIFFERENT STYLES OF COMMUNICATION

During more than 40 years different authors have study the communicative differences between men and women, and they have tried to identify the main characteristics more common in one and the other; Mulac, Studley and Blauindicate that male language is seen as more instrumental and commanding while female language is seen as more socially positive and accommodating. [53] Mulac, Giles, Bradac and Palomares point out that the women's style has been described as "*more hesitant, indirect, emotional, and uncertain"* than that of men that has been characterized as being *"more dominant, direct, and controlling"* [54].

Mulac, Bradac and Gibbons [34] did a literature review about gender-linked language differences and they identify 21 language features susceptible to be considered as indicative of the communicator gender; they separate the findings in 3 groups:

- Male language features: those found to be used more by male than by female communicators.
- Female language features: those found to be used more by female than by male communicators.
- Equivocal language feature: those found in some studies to be more indicative of males, and in others, more indicative of females.

From the 21 language features, 16 were identify as indicative of the communicator gender: 6 of the masculine style (reference to quantity; judgmental adjectives; elliptical sentences; directives; locatives; and "I" references) and 10 of the feminine style (intensive adverbs; references to emotions; dependent clauses; sentence initial adverbials; mean length sentence; uncertainty verbs; oppositions; negations; hedges; questions). About the other 5 language features (personal pronouns, tag questions, fillers, progressive verbs and justifiers) seems to don't be consensus and some studies associate them to a masculine style and others to a feminine one.

Another literature review about the characteristics associated with masculine and feminine communication styles, done recently by Weinberg, Treviño and Cleveland, they highlighted 4 key facets of each styles, about the masculine communication the 4 characteristics that they underlined were: assertive, egocentric, abstract and instrumental, while the 4 characteristics

of the feminine communication were: egalitarian, compassionate, concrete and relational. [55] Following tables synthesize their findings (tables A.1 and A.2):

Table A.1. Key facets of the gendered communication construct. Facet I: Masculine communication

Assertive	Communicate in a direct and assertive manner; communicating in a dominant, forceful, or aggressive way	Give orders in an attempt to control others (Weiss & Sachs, 1991); exhibit superiority, control by giving advice (J. T. Wood, 2013); aggressive and direct (Pearson, 1981); communicate in a way that is more forceful and authoritative (Mulac, 2006; W. Wood, Christensen, Hebl, & Rothgerber, 1997); assertive form of communication (Leaper & Ayres, 2007; Palomares, 2012)
	Dominate the conversation; interrupt others to gain command of the conversation	Communicate to assert control over others (Messner, 1997); compete for the *talk stage* or for conversational command; reroute conversations; challenge other speakers (J. T. Wood, 2013); talk often and at greater length than others (Mulac, 2006); dominating discussions (Borisoff & Merrill, 1985); usurp conversation (Tannen, 1990)
Egocentric	Emphasize and defend one's own thoughts and beliefs	Use communication to emphasize your ideas, opinions, and identity; preserve one's independence (J. T. Wood, 2013)
	Use communication to draw attention to oneself and to one's own ideas	Communicate to get attention and to stand out (Messner, 1997); use communication to attract and maintain others' attention and stand out (J. T. Wood, 2013); self-promotion (Tannen, 1994b)
	Use communication to establish and enhance one's own status	Communicate to compete for and maintain status (Messner, 1997); competitive (Leaper & Ayres, 2007); issue commands and compete for status (Goodwin, 1990); conversation as an arena for proving oneself and negotiating prestige (J. T. Wood, 2013)
	Use communication to assert one's authority	Communicate in a manner that is strong and ambitious (Kimmel, 2005); influences others (Palomares, 2012)
	Avoid disclosing personal information that might suggest weakness or vulnerability	Tendency to protect oneself from potential vulnerabilities by withholding or concealing personal information that may be construed as weakness (Saurer & Eisler, 1990)
Abstract	Use an abstract communication style, speaking in terms that are removed from concrete experiences	Impersonal (Newman, Groom, Handelman, & Pennebaker, 2008; Pearson, 1981); speak in abstract, general terms that are distanced from personal feelings and experiences (J. T. Wood, 2013)
Instrumental	Communicate in an instrumental way (as a means to accomplish goals)	Instrumental (Deaux & Major, 1987; Leaper & Ayres, 2007); communicate to accomplish goals (Messner, 1997); use talk to accomplish or achieve objectives (J. T. Wood, 2013)

Source: taken from "Gendered Communication and Career Outcomes: A Construct Validation and Prediction of Hierarchical Advancement and Non-Hierarchical Rewards" [55], with authorization of Frankie J. Weinberg.

Table A.2. Key facets of the gendered communication construct. Facet I: Feminine communication

Egalitarian	Employ a collaborative communication style	Foster cooperative and open-ended discussion (Campbell, 1993); cooperate with others (K. Robertson & Murachver, 2003; Weiss & Sachs, 1991)
	Communicate in a way that strives to establish equality among all participants	Use communication to establish egalitarian relations with others; establish equality and achieve symmetry (Ashcraft & Mumby, 2004; J. T. Wood, 2013)
	Communicate one's support for others	Demonstrate support to show understanding of others' situations or feelings (J. T. Wood, 2013)
	Communicate in a responsive way (e.g., by smiling or nodding)	Smile more frequently (LaFrance, Hecht, & Paluck, 2003); respond to others' ideas; nod or say "tell me more," or "that's interesting" (J. T. Wood, 2013); this type of responsiveness reflects a tendency to care about others such that they feel valued and included (Chatham-Carpenter & DeFrancisco, 1998), affirming the other person's position while also encouraging the other person to elaborate (J. T. Wood, 2013)
	Invite others to participate and encourage them to elaborate on their thoughts	Receptive (Pearson, 1981); include others and bring them into the conversation (J. T. Wood, 2013); use inclusive, nondirective language (Goodwin, 1990); engage in conversation to learn about others (F. Johnson, 1996); engage in participatory interaction in which participants respond to one another and build on each others' ideas (Hall & Langellier, 1988); conversational *maintenance work*—attempt to sustain conversation by inviting others to speak and by prompting them to elaborate their ideas (Taylor, 2002; J. T. Wood, 2013)
	Regard communication as a way to build rapport (harmonious connections) with others	Mindful of the *relationship level of talk*, with a focus on the relationship between communicators (MacGeorge, Gillihan, Samter, & Clark, 2003; J. T. Wood, 2013), conciliatory (Pearson, 1981); affiliative communication, promotes closeness (Leaper & Ayres, 2007; Palomares, 2012)
Compassionate	Communicate in a way that expresses empathy or sympathy toward others; understanding of others' perspectives	Concern with people and relationships (Spence & Buckner, 2000); communicate in a way that regards others' feelings and shows sensitivity to others (J. T. Wood, 2013)
	Communicate in a compassionate way; a way that is sensitive to the needs of others	Compassionately provide emotional support (Lilius et al., 2008; Miller, 2013); femininity is deferential (Spence & Buckner, 2000); employ tentative, provisional communication that allows others the opportunity to respond and express their opinions (J. T. Wood, 2013); use of tentative communication reflects the desire to maintain an open communication (Mills, 1999); polite (Pearson, 1981); consider others' points of view (Tannen, 1994a)
Concrete	Use a more concrete communication style, providing details, disclosing personal information, and using concrete reasoning	Utilize a personal, concrete style which includes details, personal disclosures, and concrete reasoning to cultivate a close, personal connection (Ashcraft & Mumby, 2004; Hall & Langellier, 1988; J. T. Wood, 2013). Share themselves via conversation (F. Johnson, 1996; Weinberg & Locander, 2013)
Relational	Communicate as a primary way to establish and maintain relationships	Communicate to create and maintain relationships; recognize that the communication process, more so than its content, is the heart of relationships; talk is the essence of relationships (J. T. Wood, 2013); promote closeness (Palomares, 2012); use words related to social processes (Newman et al., 2008)

Source: taken from "Gendered Communication and Career Outcomes: A Construct Validation and Prediction of Hierarchical Advancement and Non-Hierarchical Rewards" [55]*, with authorization of Frankie J. Weinberg.*

Mohindra and Azhar [56] indicate that *"men and women communicate on different levels and their communicational approaches are also different"*; they summarize some of these differences in the following table (table A.3):

Table A.3. Levels of Communication between Men and Women

S.No	Men	Women
1	Men keep their problems to themselves and don't see the point in sharing personal issues.	Women are more likely to talk to other women when they have a problem or need to make a decision.
2	Men tend to relate to other men on one-up and one-down basis. Status and dominance is important.	They are more relationship oriented, and look for commonalities and ways to connect with other women.
3	Men focus on talking and providing information rather than asking questions. They share experiences as a way of being one-up.	They focus on building rapport, by sharing experiences and asking questions.
4	Men can have a disagreement, move on to another subject and go get a drink together	If women have a disagreement with each other it affects all aspects of their relationship.
5	Men build relationships while they are working on tasks with each other.	Get things done at work by building relationships.
6	Men move to solutions and problem solving right away.	Women want to talk about the problems and solve them collaboratively.
7	For men asking for help reflects an inability to achieve on one's own merit.	Offering help and advice is a sign of care.
8	Men listen to the main points. They are selective listeners.	They listen to each and every word; they show attentiveness through verbal and non-verbal cues.

Source: Taken from "Gender Communication: A Comparative Analysis of Communicational Approaches of Men and Women at Workplaces". [56]

A.4.2.1 The gendered styles: the reflection of differences of role. The "report talk" and the "rapport talk".

To show the main differences between the distinctive communication style of the public and private spheres, which have been related to how men and women tend to communicate, Tannen coined the terms *"report talk"* and the *"rapport talk"*. The main characteristics of these styles are:

- Report talk (public speaking): Griffin, Ledbetter and Sparks [50] define it as *"the typical monologic style of men, which seeks to command attention, convey information, and win arguments"* and points out that *"men use talk as a weapon"*. Eunson indicates that is a task-oriented talk that seeks to produce solutions. [57] Tannen explains that "*this is done by exhibiting knowledge and skill, and by holding center stage through verbal performance such as storytelling, joking, or imparting information"* [31].
- Rapport talk (private speaking): Griffin, Ledbetter and Sparks define it as *"the typical conversational style of women, which seeks to establish connection with others"* [50]. Eunson indicates that is a relationship-oriented talk that seeks to build understanding and empathy within a wider group. [57] Tannen points out that its emphasis is on displaying similarities and matching experiences. [31]

In a similar way than Tannen, connecting men's and women's style of communication with the ambit and role that society assign to each gender, Eagly and Carli indicate that women are

associated with communal qualities and men to agentic qualities, saying that *"women are associated with communal qualities, which convey a concern for the compassionate treatment of others. They include being especially affectionate, helpful, friendly, kind, and sympathetic, as well as interpersonally sensitive, gentle, and soft-spoken. In contrast, men are associated with agentic qualities, which convey assertion and control. They include being especially aggressive, ambitious, dominant, self-confident, and forceful, as well as self-reliant and individualistic"* [58].

A.4.2.2 Constructing the discourse

Tusón describes the differences between feminine and masculine style constructing the discourse, she highlights that in the feminine style is done in a shared way, with more involved and personalized style, whereas men have the tendency to summarize or reformulate what is being said and to use a more assertive style. [14]

She also indicates that feminine style is characterised by using more the second person and the first person of plural, to include the people they speak with; while masculine style use more the first person singular, third person and impersonal forms. Hirschman found this fact correlated with the stereotype that says that females usually talk more about their own experience and feelings while men use talk abstractly and generalize more. [59]

Tusón also indicate that feminine style uses more often interrogative and exclamatory sentences and less frequently enunciative sentences than the masculine style. Feminine style also uses more indirect and less imposing forms and leaves more unfinished sentences than masculine style that uses more direct statements. [14]

Hirschman points out that most voluminous female speakers use more affirmative responses and fillers than most voluminous male speakers, she posits that this may be done to compensate their possible aggressiveness by increasing hesitancy and through greater responsiveness to the person she speaks with. [59]

Hirschman also suggest that, when talking with somebody they don't know, women feel more comfortable and talk more easily to another woman than to a man, she didn't suggest any preference in males. [59]

Mulac, Studley and Blau indicate that female speakers are more likely to begin the sentences using adverbs or adverbial sentences and to use longer sentences; while male speakers are more likely to make grammatical errors and use judgmental phrases. [53]

A.4.2.3 Telling a story

Tannen indicates that men tell stories more often than women do and they do it more frequently speaking about themselves, whilst is more habitual in women than in men to tell stories referring to others. When men speak about themselves, sometimes they take the role of protagonist and antagonists, and usually they do it making them look good; when women

talk about themselves usually present them doing something foolish. [31] [50] Johnstone (mentioned by Tannen) found that the protagonist of men's stories, when is not about themselves, usually is about other men, being strange that they tell stories about women, while women stories are about themselves, men or other women. [31]

A.4.2.4 Telling jokes

Men usually tell more jokes than women, and they prefer to do it when they have an audience, doing it even when it includes people that they don't know well; men tell jokes usually to other men, but also to women or to mixed groups. Women usually prefer to do it in small groups (rarely more than three people) and the ones who tell jokes to large groups usually come from ethnic backgrounds in which verbal performance is appreciated; when women tell jokes usually is to other women, being strange that they tell them to groups of men and even less common to do it to mixed groups [31].

A.4.2.5 Gossip and "sport-talk"

Gossiping is a term used mostly related to women's talk and usually in a pejorative way. Jones (quoted by Coates) uses this term in a positive sense and defines it as *"a way of talking between women in their roles as women, intimate in style, personal and domestic in topic and setting"* [60]. Coates points out that the use of the term gossip brigs the idea of a talk between women in a non-serious way, in contrast with the men's talk that is seen as a real talk and always serious; but the truth is that gossiping it is *"a process vital to everyday life and not restricted to women"* [60]. In fact, a report published by The Guardian quoted a study indicating that *"some 27% of men, compared with 21 % of women, admitted making calls primarily for gossip, which 26% of men referred to as "keeping in touch". But when some were questioned in focus groups, this often proved to be "essentially a euphemism for gossip""* [61].

Several authors have highlighted the importance of the gossip, for example Holmes indicates that *"gossip conveys information - about people, events, attitudes - as well as serving the cohesive social function of emphasising membership of the in-group and reinforcing solidarity between contributors"* [51].

Cameron identifies *"sports-talk"* as a typical masculine conversational genre, and indicates that it has a similar purpose than gossip between women. [60] Several authors link the sports-talk with the gossip, for example Moss wrote an article in The Telegraph entitled "*Welcome back football, the great gossip mag for men. Prowess, professionalism, technique, talent? Forget it. Professional football has become the male equivalent of Hello! magazine"* [62] that shows how men gossip about all that involves football (live of the players, conflicts between them, what they say or post in the social media…). Johnson and Finlay, quoted by Coates, indicate the importance of talking about football and the importance of its role, saying that *"if female gossip is a way of talking which solidifies relationships between women, then talking about football would appear to serve a very similar purpose for men"* [63]. Benwell indicates that men's lifestyle magazines also play this same role, and indicates that in both cases (men's

lifestyle magazines and football talk) the gossiping is limited to unknown and famous individuals, avoiding personal experiences and private sphere. [64] In fact this is one of the differences that Coates highlights between the men's talk that can be labelled as 'gossip' and women's gossip, because women's gossip is focus in the personal experience; other difference that she identifies is the competitive element that always appears in men's talk. [60]

A.4.2.6 Choosing a topic

Johnstone, quoted by Tannen, found differences about the topic that men and women choose for their stories, women usually choose topics about community while men do it about contest. (31) Bischoping indicates that women talk more than men about people and relationships and appearances, while men do it more than women about social and political issues, work, money and leisure activities, especially sports. [65]

Tusón indicates that usually women change the topic more often than men and they usually treat the topics from their own intimate experience, while men use to keep the same topic for longer and treat them from an external point of view. [14] Nevertheless, Eunson points out that men change the topic more than women and he specifies that to change the topic women use more conjunction as "however", "but" or "and", while men use more interjections as "oh", "by the way" or "listen". [57]

Fishman indicates that women try more often to introduce topics in the conversations than men but are less successful; these are considered tentative and discarded easily, while the topics proposed by men are seen as topics to be pursued. [27]

A.4.2.7 Talking about troubles: "Trouble talk"

Tannen coined the term *"trouble talk"* and considered it as a particular type of rapport talk. She found that when women talk about troubles they seek for connection, reaffirm mutual interests, exchange points of view, share experiences and to get closer, as Alami [33] says *"I tell you my troubles, you tell me your troubles, and we are close"*, they give sympathy and expect the same in response [66], without the necessity of looking for a solution, on the other hand men understand the trouble talk as a request for advice where the main aim is to look for a solution [31] [33] [50] [57]. These different understanding of troubles talk bring different ways to respond, usually men do it giving advice, joking, changing the subject or giving no response while women respond more sharing a similar problem or expressing sympathy; these differences also bring up conflicts because, as Michaud and Warner say, "*when men respond to women's troubles talk by offering advice, women tend to feel that their feelings are being invalidated, their problems are being minimized, or that their partner is being condescending by telling them how to "fix" the problem. Conversely, when women offer sympathy to men, men may feel that they are being placed in a one-down or lower status position and being condescended to*" [66].

A.4.2.8 Minimal responses

Maltz and Borker identify differences of interpretation in the use of minimal responses in the conversation interaction between genders, such nods and comments likes "*yes*" or "*mm hmm*", indicating that when women use it means something like "I'm listening to you; please continue", and when men do it means "*I agree with you*" or "*I follow your argument so far*", so the fact that women use minimal responses more is because they listen more often that men agree. This makes that [23]:

1- *"Men who think that women are always agreeing with them and then conclude that it's impossible to tell what a woman really thinks.*
2- *Women who get upset with men who never seem to be listening"*

Hirschman's findings coincide with what Maltz and Borker said about women using more often minimal responses than men, but also point that they use them more when are speaking with another woman [59].

Nevertheless Fishman gives other sense to the use of the minimal responses by men, she says that *"male usages of the minimal response displayed lack of interest. (…) Such minimal responses are attempts to discourage interaction",* women also do sometimes that use, but the most common use is as "support work" showing her participation and interest in the interaction and the speaker [27].

A.4.2.9 Hedges

Several authors have shown that women use hedge more frequently than men and this has influenced in considering women's speech as "tentative"; Lakoff for example linked the use of hedges with unassertiveness and lack of confidence. However, Coates draws attention to the functions that use of hedges[j] have, for example, she mentions that the hedge "*you know*" can be used to express confidence or uncertainty, and a research done by Holmes show that women use it more often to express confidence while men use it to express uncertainty. She also posits that the lower use of hedges by men is because of the choice of topics: men avoid sensitive topics and prefer to talk about impersonal subjects; indicating that the use of hedges is more usual (and very value) in sensitive topics because mitigates the force of what is said. [60]

A.4.2.10 Silent, interruption and overlapping

Zimmerman and West [24] indicate that there is an asymmetry in the conversational relations between men and women and this was reflected in the patterns of interruption silent and support, and they observed that:

[j] Coates defines "hedges" as a "linguistic forms such as *I think*, *I'm sure*, *you know*, *sort of* and *perhaps* which express the speaker's certainty or uncertainty about the proposition under discussion" [60].

- Men interrupt more than women.[k]
- Women fall silent (strategy of "silent protest") when:

    a) They are interrupted by men;
    b) After a delayed "minimal response" by men;
    c) Men overlap them.

- Men don't fall in silence when they are interrupted by a woman.

Griffin et al. explain that when women start to speak before her conversation partner finished usually is to show her agreement, solidarity or to finish the sentence with what she thinks the speakers want to say, doing what Tannen called a "*cooperative overlap*". This cooperative overlap is seen by women as a sign of rapport instead of an intent to control the conversation, but from men's point of view any interruption is competitive, is a power move to control the conversation so the cooperative overlaps usually annoys them. (50)

A.4.2.11 Asking questions

Several authors point out than women ask more questions than men, for example, Hirschman indicates that "*several of the female/male conversations fell into a question-answer pattern, with the females asking questions and the males answering, but not asking the females questions in return*"; she relates it to the role of women as facilitators of the conversation. (59) Fishman, in the same direction, points out that women usually work more in the conversations and take a more active role in insuring interaction than men, and she puts as example asking more questions. (27)

Tannen (31) indicates that this perception (women ask more questions than men) is not real and it depends on the sphere where the conversation is taking place, in private sphere women ask more than men, but in public sphere men are the ones who ask more, for example she says that in public lecturers *"men almost invariably ask the first question, more questions, and longer questions"*. She also points the differences about men's and women's questions, using an example of students asking her questions (she as an expert), she realised that women's question were supportive or exploring while that of men were challenging.

Túson (14) indicates that feminine style includes more questions "*echo*" (*isn't it?, right?, huh?, don't you think?..*) than the masculine style. On the same subject, Lakoff (20) thinks that tag-questions (*isn't he?, don't you?, isn't it?...*) are more apt to be used by women than by men, and she explains that using these kind of questions speakers avoid to compromising and coming into conflict with the person she/he is speaking with, but also gives the impression of insecurity. Tannen (31) indicates that people expect women to use tag-questions and when

[k] Zimmerman and West identify the interruption as a *"violation of a speaker's right to complete a turn",* they also observed a lesser extent asymmetry in overlaps, that they understood as "*errors indigenous to the speaker transition process*".

they have to guess the sex of the person speaking, they usually take the presence or absence of tags as an important clue (if tags are used they usually say that it is a woman and if there isn't they say that is a man); she also points out that women who use tag-questions and disclaimers are considered less intelligent than men who used them. Mulac, Bradac and Gibbons [34] identify the use of tag questions as an equivocal language feature, because some studies considered that men use them more often than women; that studies were in the context of an academic conference participation and in informal conversations between students. Crawford [67] also highlights that there is not a consensus about considering or not tag questions as a characteristic of a gendered style and describes Lakoff's claim as oversimplified.

Fishman [27] indicates that women use twice more often than men the kind of questions "D'ya know what?" that is a sequence Question-Question-Answer *("D'ya know what?" "what?" "Blahblah (answer)"*) very used also by children and that is a way of insuring rights to speak.

A.4.2.12 Paralanguage: Prosody

Túson [14] describes the following prosodic characteristics of the feminine and masculine styles:

- Feminine style is distinguished by a more emphatic intonation, with a lengthening of the vowel and using more intonational modulations, while masculine style has a more staccato rhythm with fewer intonational modulations.
- Feminine style includes more changes of tone of voice than the masculine style, with tendency of using more acute tones.
- Feminine style use ascending endings whilst masculine style includes descending endings.

McQuiston and Morris indicate that is usual that women raise their voice's tone in response to a question, mainly at the end of the sentence, as in a question-like statement (for example, the man ask "What would you like to eat?" and the woman replies "A pizza?"), probably they do this to indicate support or to don't bring any inconvenience to the other person. [68]

A.4.2.13 Vocabulary

As Túson [14] describes there are differences in the vocabulary used in feminine and masculine style. Feminine style is characterised by the use of vocabulary related to private areas as family, home or affections, among others; by using more words that designate nuances as for example when referring colours; and to use more diminutives and words that express affection. On the other hand the male style characteristically uses vocabulary related to the public areas as politics, sports or work, among others; to use more coarse vocabulary as swearwords; and to use the augmentatives.

McQuiston and Morris indicate that women use more intensifier adverbs (as *very*, *really* or *vastly*) than men, and they think this can be to *"better express emotion and power"*. They also explain that its use usually seeks to emphasize an aspect of their statement or to give credibility to it. [68]

Eunson point out that men use more quantifiers (as *always*, *never*, *all* or *none*) than women, while women use more qualifiers (as *kind of* or *a bit*) than men do. He also highlights the aggression as other characteristic of the men's style of communication and indicates that *"men may be more likely to use profanity/obscenity, and to use teasing insults and playful put-downs either as indicators of affection and intimacy or as threatening and controlling behaviour"* [57].

A.4.2.14 Politeness

Many authors point out that women speak more politely than men and they use less 'vulgar language'. For example, Lakoff indicates that *"women's speech sounds much more 'polite' than men's"* [20] and considers that one aspect of this politeness is not to impose your mind/views/claims on anyone else, leaving an open decision and she notes that the use of tag-questions is very useful for this, as it doesn't force agreement on the addressee.

As it has been written in the explanation of the dominance approach, several authors relate the more politeness of women as a reflection of the social differences and power. As we said before, Brown explains the more politeness of women because they are "*culturally relegated to a secondary status relative to men and since a higher level of politeness is expected from inferiors to superiors"* [25]. In the same direction Cameron [26] points that men aren't more polite because they feel that they don't need it. Holmes also talks about the relationship between politeness and subordination and use it to explain the fact that women are more polite than men. She also differentiates two types of politeness: *"positive politeness that is solidarity oriented. It emphasises share attitudes and values (…). By contrast, negative politeness pays people respect and avoids intruding on them. Indirect directives (…) express negative politeness*" (69).

McQuiston and Morris [68], as Holmes [69], indicate that women are more polite and men more directive in communication.

A.4.2.15 Compliments

Coates says that several researches indicate that women give and receive more compliments than men, she also offers some details about different studies that are summarise in the following points: [60]

- The majority of compliments are given by a woman to another woman, being not common the ones given by a man to another man. When a man gives a compliment usually is to a woman, in fact men use to give compliments to women more often than

vice versa. The compliments given by one woman to other are quite common and usually are about appearance, while between men usually are about possessions or skills and they normally avoid the ones about appearance (that are more common between gays).

- Women use more personalised compliments forms (with first or second person focus, e.g. I like your shoes or your hair looks good) while men preferred impersonal ones (third person focus, e.g. nice shirt!).
- Holmes indicates that *"compliments are remarkably formulaic speech acts. Most draw on a very small number of lexical items and a very narrow range of syntactic patterns*" and the patters followed by men and women are similar, with differences in the forms "*What (a) ADJ[Adjective] NP[Noun Phrase]*" (e.g. What lovely earrings!) that is more used by women and the minimal pattern (e.g. Great shoes!) more commonly used by men.
- Herbert found that between two people with different status is expected that the person with higher status gives the compliment and the one with lower status accepts it.

A.4.2.16 Non-verbal communication

Mulac, Studley and Blau [53] point out that there are differences about how men and women use the nonverbal language, and these differences are consistent with gender stereotypes, as examples of these differences they mention that women tend to smile and gaze more, while men overlap more and tend to speak in longer sentences. Mohindra and Azhar [56] say that women are better interpreting non-verbal communication than men.

McQuiston and Morris [68] indicate that women smile more often than men do and they considered that they do it as part of their role, in fact men smile when they are happy or amused while women do it even if they don't feel any positive emotion. They also indicate that women usually nod more than men, as a signal of agreement. Men gesticulate more when are talking but they show less emotions, remaining more neutral, and even to seem more neutral they use facial expressions less often.

Tusón [14] identifies some kinesics differences between the feminine and masculine styles. She indicates that in the feminine style the physical contact is smoother, being more usual actions like holding the arm while walking or kissing in the greetings and with more proximity when speaking. In masculine style physical contact are more sporadic and aggressive, with actions as blows, pats or hand clash in the greetings and keeping greater distance when speaking. McQuiston and Morris [68] indicate that women feel more comfortable than men in the side-by-side interaction.

Tusón [14] also indicates that in feminine style the hands and arms gestures are usually done in a space closer to the body (with the forearm almost close to the chest) while in masculine

style the arm and hands gestures are wider. And in feminine style legs usually are together or crossed by knees while in masculine style legs are open or crossed with one foot on one knee.

Hall and Friedman [70] indicate that there exist several differences on nonverbal behaviours and skills between men and women, mentioning "*smiling, gazing, nodding, expressiveness, self-touching, gesturing, use of verbal facilitators, interruptions, and accuracy in the decoding and encoding of nonverbal cues*" as example of these differences. Authors such as Henley suggest that these differences are explained by status/dominance differences, but Hall and Friedman argue that finding a parallelism between status and gender effects is not enough to infer a causal relation, and they suggest that these differences probably will be a product of socialization factors. They indicate that status can have different effect on men and women; in fact, they studied the differences in nonverbal communication taking into account status and gender, and found that higher status men used more facilitators and fewer interruptions and higher status women were more active nonverbally, which can be said as more "open", confident, and supportive; they were characterized by being warmer and more expressive; more nodding, gazing, gesturing, and touching; and fewer facilitators.

McQuiston and Morris [68] highlight the importance of the eye contact and how it reflects patterns of perceived social domination, and indicate that higher status people maintain the eye contact more when they are speaking while the lower status people do it more when they are listening to a person with higher status. Traditionally the role of lower status is associated with women and higher status with men. Mohindra and Azhar [56] point out that men are not so comfortable as women with the eye contact, and they suggest that it can be because of the considerations about power, status and dominance; they also identify direct eye contact as an indication of emotion.

Is important to remember that there are differences not only in how men and women communicate, but also in how people communicate to them, also reflected in non-verbal communication, Hall and Roter [71] indicate as examples that people gaze and smile more to women or approach to them more closely. They suggest that in social interaction it seems that women are different stimulus than men, and they also point out that some behaviour, as smiling, gazing, some postures or tones are reciprocated.

Eunson, in his book *"C21 Communicating in the 21st century"* [57], compiles the main gender differences in non-verbal communication from several authors (Lakoff; Glass; Tannen; Gray; Gamble and Gamble; Stewart, Cooper, Stewart and Friedley; Pearson, Turner and Todd-Mancillas; Trethewey)[l].

[l] Chapter 7, pages 14 and 15 (Table 7.2: Gender differences in non-verbal communication).

A.4.2.17 Written

Most of the differences already shown in the general communication differences also appear in written style.

Mulac, Giles, Bradac and Palomares [54] in a research about the gender-linked language effect[m] studied the difference between men and women written style, the existence of genderlinked language stereotypes and the accommodation to the gender of the reader. To do so they asked the participants to describe different photos, first without any special instruction (gendered style), after other photos ''as if you were a man'' and ''as if you were a woman'' (genderlinked language stereotypes) and finally other photos ''for a man'' or ''for a woman'' (accommodation), from their findings they realize that:

- Gendered style: masculine written style includes more references to quantity; sentence initial adverbials; ''I'' references and elliptical sentences. Feminine written style uses more number of words and references to emotion.
- Genderlinked language stereotypes: masculine written style is considered to use more elliptical sentences, references to quantity and negations. While feminine written style is considered to use more references to emotion; judgmental adjectives; sentence initial adverbials and a bigger number of words.
- Accommodation: the analyses didn't show any communication accommodation, so they didn't found evidences of the accommodation of the text to the gender of the reader.

Eunson [57] points out that female writers focus more on relationship than on the task topics; they use the written channel in a similar way than the face-to-face or the telephone conversation, to build relationships, maintaining friendship and kin networks. Similar tends appear in the fiction and non-fiction texts where female writers use a more personal or involved style while male use a more informational and detached style.

Mulac, Studley and Blau identified for their research *"The Gender-Linked Language Effect in Primary and Secondary Students' Impromptu Essays"* [53] 19 language variables as potential predictors of writer's gender. They also analysed previous empirical studies to determine whether these variables were considered indicative of male or female communicators, obtaining the following information[n]:

[m] Mulac, Giles, Bradac and Palomares describe the gender-linked language effect as a "phenomenon in which transcripts of female communicators are rated higher on Socio-Intellectual Status and Aesthetic Quality and male communicators are rated higher on Dynamism"

[n] The original article can be consulted to see the researchers that have found each variable as indicative of male or female communicators.

1. Sentences:

- Mean length sentence (number of words/number of sentences). Four empirical studies found it more indicative of female communicators.
- Use of rhetorical questions (apparently don't expect any response). One empirical study found it more indicative of female communicators.

2. Clauses an phrases:

- Sentence initial adverbials (answering the questions How? When? Or Where? regarding the main clause). Two empirical studies found it more indicative of female communicators.
- Relative clauses (specify or qualify the words that convey primary meaning). Two empirical studies found it more indicative of female communicators and one of male communicators.
- Oppositions (retracting a statement and presenting one with the opposite meaning). Two empirical studies found it more indicative of female communicators.
- Judgmental phrases (personal evaluations more than descriptions). One empirical study found it more indicative of female communicators, while another one found it more indicative of male communicators.

3. Verb phrases:

- Action verbs (indicating movement or actions). One empirical study found it more indicative of female communicators, while another one found it more indicative of male communicators.
- Uncertainty verbs (indicating lack of certainty). Two empirical studies found it more indicative of female communicators.
- Progressive verbs (-ing forms). One empirical study found it more indicative of male communicators.

4. Modifiers

- Hedges/Softeners (indicate lack of confidence). One empirical study found it more indicative of female communicators.
- Intensive adverbs. Six empirical studies found it more indicative of female communicators.
- Justifiers (give a reason to a previous assertion). One empirical study found it more indicative of female communicators, while another one found it more indicative of male communicators.

5. Conjunctions

- Coordinating conjunctions (connects elements grammatically similar). One empirical study found it more indicative of male communicators.

- Subordinate conjunctions (connects elements grammatically different). One empirical study found it more indicative of female communicators.

6. References

- To emotion or feeling. Three empirical studies found it more indicative of female communicators.
- To quantity or place. Five empirical studies found it more indicative of male communicators.

7. Miscellaneous

- Grammatical errors. Two empirical studies found it more indicative of male communicators.
- Fillers (words used other than for their semantic meaning). Two empirical studies found it more indicative of female communicators and one of male communicators.
- Contractions (condense two words into one using an apostrophe to sign the omitted letters). They didn't found any previous study that considered it as indicative of writer's gender.

In the last 15 or 20 years different authors have tried to design algorithms to predict the gender of the writer of a text. Koppel, Argamon and Shimoni indicate that *"it is shown that automated text categorization techniques can exploit combinations of simple lexical and syntactic features to infer the gender of the author of an unseen formal written document with approximately 80 per cent accuracy"* [72], so they defends that there are differences in the way men and women write that reflects in the use of different kind of words (as prepositions, singular nouns or articles) or even the punctuation marks.

Ishikawa [73] did a research analysing of the written argumentative essays done by university students about two topics given and she found gender differences in language that suggest that *"male students tend to use more nouns related to social economic activities to convey information or facts about the given topics, whereas female students tend to use more pronouns, more intensifiers and modifiers, and words related to psychological cognitive processes so that they might convey their feelings and develop a good relationship with other people"*. Her study also included the following table that summarize the findings of the studies done by Koppel, Argamon and Shimoni [72]; Argamon, Koppel, Fine and Shimoni [74]; and Newman, Groom, Handelman and Pennebaker [75] (table A.4).

Table A.4. *Summary of gender differences revealed by Koppel et al., Argamon et al. and Newman et al.*

	Male	Female
Koppel et al.	noun specifiers (*that, one*)	negation (*not*), pronouns, prepositions (*for, with, in*), conjunction (*and*)
Argamon et al.	determiners (*a, the, that, these*), quantifiers (*one, two, more, some*)	pronouns (*I, you, she, her, their, myself, yourself, herself)*
Newman et al.	numbers, articles, prepositions (on, to, from)	pronouns (*I, my, me, she, their, them*), social words (*sister, friends*), psychological processes (mad, uneasy), verbs, negations, references to the home (*home, house*)

Source: Taken from "Gender Differences in Vocabulary Use in Essay Writing by University Students" [73]

A.5. GENDER DIFFERENCES IN SKILLS

Several studies point out that men and women have different comprehension skills; some of these researches follow a biologist approach that puts the focus on the sex differences (biological and anatomic differences), while others are done under a gender perspective, explaining the differences as effects of social and cultural processes. In this document we focus only in the studies done under a gender perspective and we use as main references the PISA and the PIAAC survey, as there are some of the most quoted main referred criteria used in most of the studies.

Most of the studies in this field are done to scholar population and are based in the stereotypes and hold that males are better in mathematics and spatial tests, and females on verbal tests. [76]

A.5.1 Gender differences in scholars: the PISA survey

The Organisation for Economic Co-operation and Development (OECD) has the Programme for International Students Assessment (PISA) that includes a triennial survey to 15-years-old students from different countries around the world; this survey assesses the acquisition of some key knowledge and skills, focusing on the core school subjects of science, reading and mathematics and it also asses the proficiency in an innovative domain, changing the specific topic in each survey, for example in the 2015 survey it was on collaborative problem solving. The PISA survey is one of the most widely used criteria for assessing the quality, equity, and efficiency of school systems and the skills difference among students [77].

The OECD did in 2015 a special report about gender differences using the data of the PISA survey (and punctually the Survey of Adult Skills), some of them are [78]:

- Overall achievement: Is more likely that boys get lower achievers overall than girls, in fact a higher proportion of them don't arrive to the level of proficiency in any of the three main subjects (science, reading and mathematics). This probably is explaining because they spend less time studying and doing homework outside school.
- Reading: Girls usually have better skills than boys in reading; these differences are narrower when reading in digital format. A possible explication for these differences is that for enjoyment girls read more than boys, especially complex books as fiction, while boys spend more time than girls playing video games. Is important to remark the importance of reading proficiency, because is the base where all other learning is built; so it affects their performance in other school subjects, as Merisuo-Storm [79] indicates *"good readers are better students than poor readers in every subject area"*, and she also points out that habitual reading has a positive influence on writing and reading skills.

- Mathematics: Usually boys do it better in mathematics than girls. Girls are less confident in their ability to solve mathematics or science problems than boys and they

express strong feelings of anxiety towards mathematics more often. These differences disappear between boys and girls with similar levels of self-confidence in mathematics and of anxiety towards mathematics.

- Thinking like a scientist: Girls do it better solving mathematical or scientific problems when the task is similar to the ones that they routinely do in school, but they do it worse than boys when they are required to "think like scientists". Boys usually have better results than girls when they have to apply their knowledge of science to a given situation, describing or interpreting phenomena scientifically and predicting changes. These differences may be related to the self-confidence than makes them to be less worried if they fail, that is essential in the trial-and-error processes that are necessary for learning mathematics and science.
- Cause of the differences: The OECD points out that these differences are caused by gender differences and not by sex ones saying that *"PISA shows that gender gaps in academic performance are not determined by innate differences in ability"* [78].

A.5.1.1 Other contributions to this topic

To explain these gender gap differences is also interesting to draw on the narrative review done by Meece, Glienke and Burg [80] about gender and motivation, were they highlighting the importance of stereotypes in the development of the skills, indicating that gender stereotypes have an important influence in the motivation-related beliefs and behaviours of boys and girls; usually boys have more favourable motivation to the areas of mathematics, science, and sports while girls have it to language arts and reading; even so the gender gap in motivation in mathematics and science use to decrease with the age, while gender differences in the conception of their reading and sporty ability appears early and continues over all the schooling. They also indicate that there exist gender differences in causal attribution patterns to the success in mathematics and sciences, indicating that boys are more likely to point that their success is because of their ability while women usually attribute it to the effort.

About reading habits, Lasarte [81] indicates that girls read more books and magazines whiles boys read more newspapers, webs, blogs or forums; Merisuo-Storm [79] indicates that boys prefer comics and humorous books while girls prefer adventure books. In the survey Lasarte [81] did to 300 students of 11-12 years old from Vitoria (Basque country) she realised that girls read an imaginary world more feminine than boys. Merisuo-Storm [79] point out that at early-age children start to differentiate between ''girl book'' and ''boy book'' and boys avoid to cross that gendered boundaries more than girls, and indicates that some groups of boys consider the school literacy as ''un-masculine'' with the adversely affect that it has to their reading habit and their reading and writing skills.

Lowrie and Diezmann [82] did a research using the Graphical Languages in Mathematics (GLIM) test with 317 Australian students (169 males and 148 females) aged 9-12 years, and they found that they are gender differences in the interpretation of graphics tasks and these are wider as the complexity of the task structure (connectivity between graphic, text and

contextual information) increases, observing that boys tend to be more skilled than girls on the most difficult tasks. They also found that boys outperform girls on map language (information represented on an axis and graphical languages that required movement between 2D and 3D representations).

A.5.2 Gender differences in adults: the Survey of Adults Skills (PIAAC)

The Survey of Adult Skills, is also a product of the OECD Programme for the International Assessment of Adult Competencies (PIAAC), this survey "*assesses the proficiency of adults in three information-processing skills essential for full participation in the knowledge-based economies and societies of the 21st century: literacy, numeracy and problem solving in technology-rich environments.*" [83] This and the PISA survey use a different conceptual framework, mainly because of the characteristics of the reference population, but they still enough similar to allow a qualitative comparison between them in the field of the gender gap. [84]

The main results of this survey about gender differences are [84]:

- Literacy proficiency: the gender differences found in the PISA survey (girls are more skilled than boys) became no significant among adults in most of the countries. In the countries that still a significant difference usually this is small, and in some countries men present better scores (as Turkey, Netherlands or Spain) while in others women have advantage (as Greece or Poland).
- Numeracy: gender differences in numeracy (shown in the PISA survey in a better ability of boys in mathematics) continue appearing in adults, and men still have better results than women in numeracy tests in almost all the participant countries.
- Problem solving in technology-rich environments: in this field the gender differences are very small, men tend to have just a little advantage.
- Relation with age: Both gender gaps (literacy and numeracy) appear to have a relation with the age:
    - In numeracy it seem to be wider among older adults (25-44 and 45-65 years) and narrower between young adults (16-24 years).
    - In literacy: The gender gap found in the PISA survey narrows with the age and arrives often to reverse in older adults.
    - The OECD indicates that "*in half the countries surveyed, there is no difference between young men and young women in their proficiency in numeracy, and they are equally proficient in literacy, with young women slightly more proficient in some countries.*" [85]
    - The reason of these changes gives the impression to be caused by one hand, among the young adults, by the decrease of the gender gap in the access to the studies and, on the other hand, among the older adults, by higher

employment rates among men that gives them more opportunities to read, write and use problem-solving skills at work, improving them [78] [84].

A.5.3 Differences in gender comprehension of IC by gender

A systematic review and meta-analysis done by Tam, Huy, Thoa et al. found that gender had no effect on the proportion of participants who understood informed consent in clinical trials. By contrast other personal characteristics as age (older participants), health status (ill), educational level (lower) o country of origin (low-income) have seen to have effect on the proportion of participants who understood informed consent in clinical trials. They also highlight that no significant changes in the understanding of any components have been founded in the last 30 years. Tam also point out that some simple measures as take care of the format, do it easily readable and take time to discuss it with the participants can be more effective than more complex measure to improve the understanding. [86]

Due to the recent of this research and the methodology used not a lot of other studies non included in the systematic review done by Tam et al. have been found and the ones that have been point out in the same direction, for example Bergenmar, Johansson and Wilking did a questionnaire to 268 patients to measure the knowledge and understanding about cancer clinical trials among trial participants, and they found not differences in the understanding by gender but they also indicate non differences found by the rest of clinical and socio-economic factors studied. Is important to highlight that Bergenmar et al. found that the 'use of other information sources' and the 'time for information' (to have lasted for >30 min) as factors that where associated with a better perceived understanding. [87]

Paris, Deygas, Cornu et al. [88] did a research to measure the impact of the modification of the IC form in terms of structure and readability in the participants' understanding in 481 patients in France (241 with the original IC and 240 with the improved one), and they realised that they were not significant differences in the understanding between both groups but the group with the improved IC documents decrease their enrolment. Some gender differences were found, that point to a better understanding by females in univariate analysis and, in multivariable analysis, gender (female) and educational level were associated with a better objective comprehension, this finding is not consistent with the review that Tam et al. did, but is in the same line of other researches that haven't been included in that systematic review, as the ones of Paris, Nogueira da Gama Chaves, Cornu et al. [89]; Raich, Plomer and Coyne [90]; or Morrow, Gootnick and Schmale (in IC for treatment) [91].

Paris, Nogueira da Gama Chaves, Cornu et al. [89] did a research with 200 volunteers to compare the understanding of four versions of the Informed Consent Form (ICF), one unchanged and other three with different improvements (one with a systematic lexico-syntactic readability improvement; other one modified by a working group; and the last one modified by the working group followed by systematic lexico-syntactic improvement); and they found gender differences in understanding at baseline, when women presented better

comprehension scores than men, but as it was a secondary end-point they are cautious with this conclusion. About the improving of the comprehension by the methods used, they found that in phase I clinical trials all the improvement suggested were effective, without important differences between them, so they recommend using any of them, but not both at the same time. Non gender differences in the impact of the improvements were registered by the authors.

Morrow, Gootnick and Schmale [91], studied the effect that giving more time to read the IC for a treatment (by taking it home) had in the understanding of a ICF, and they observed by one side that in the standard manner (without taking it home) women were better informed than men in most of the areas of the informed consent (procedures; purpose; discomforts and risks; appropriate alternatives; questions answered; diagnosis), founding not differences in the treatment area; and by the other side they found a positive effect of taking it home in the improvement of the understanding, especially in men that experimented a higher improvement in all the areas except questions answered where women improved more than them and treatment area, where they didn't improve. The antiquity of this research (published in 1978) makes to be very cautious with the results, but it has been included because it gives some ideas (as the effect of giving more time for the comprehension) and reflects the understanding in a first moment.

Knepp [92] did a research with 183 students to determine if they read the IC form comparing the frequencies in on line (remote access) or in laboratory (in person), the IC form used were approximately 1,75 pages long. He realised that usually people read it more when the procedure is done in the laboratory session than if they do it online at a remote location; he also found that, in person, women use to read it more often than men do, gender differences were not found in online sessions. He also points out that women were more caution to avoid manipulation than men and he consider that these findings can be related to the fact that women tend to use more written information sources than men or that they are more wary because historically they have suffered abuse more often in this field. In his conclusions he indicates that women prefer to do the IC process face to face, so they can receive more verbal information if needed. He also highlights that women usually are more information seeking.

Lobato, Bethony, Pereira et al. [93] evaluated the gender differences in the factors influencing the participation in clinical trial through a questionnaire administered to 143 volunteers (48 male, 95 female) in Brazil. They found that they were significant differences by gender; women tend to be more influenced by friends, partner, family, the researcher and altruism than men, demonstrating the influence of other factors besides the individual characteristics, as interpersonal relationships or social norms. They also hypothesize that the influence of the partner or family members is more notably in developing countries than in developed ones. Is interesting that, as Carpenter, DeVellis, Hogan et al. [94] indicate, female potential participants are more influenced by their partners to be involved in a clinical trial, but men trust more

their partners than women in other medical decision making as for example as source of medication information.

A.6. ONLINE GENDER DIFFERENCES

The Internet is resulting in a crucial communication strategy as it is the pathway for deliver information, provide entertainment and offer online tools. (95) The increasingly prevalence of social media, including online discussion, website forums, blogs, social networking sites, etc., has created a huge platform where the audience can publish and share their reviews on products, services and experiences. (96) Online gender differences refer to the different uses of the Internet between males and females. Back in the early stages of the Internet, there were significantly more men using the Internet than women. With the development and boom of the new technologies this has significantly decreased and nowadays researchers focus on the study of the different ways that women and men use the Internet. (97) However, we do not have to forget that the study of human's behavior will never be a precise science, so results will always be inconsistent and unpredictable.

A.6.1 Gender differences in online communication

Online discussion is a way of communication that has become of high importance in the last years for all citizens of the 21st century. (98)

Online discussion has appeared to be one of the tools used for communication in a lot of different environments. Thus, it is important for researchers to know the gender differences in online learning strategies and apply them to design better online discussion environments. (98)

Results from a study that compare university student's discussion strategies in online and face to face (F2F) contexts within the following factors: comprehension, interaction, elaboration and anxiety; showed that females tend to have better elaboration skills than male in online discussion contexts while in face to face context males and females seem to have similar levels of discussion strategies. Also, young females have higher Internet self-efficacy in online communication than young males, maybe due to their better online elaboration strategies. Regarding the change from F2F to online discussion methods, the study has shown that females are better adapters than male students because the females are more disposed to develop advanced interactive strategies to comprehend and elaborate ideas in online discussions, which may be related to the fact of women self- efficacy of using the Internet as a communication tool. Another important aspect is that online discussion strategies have shown to reduce both gender's anxiety due to less social pressure, interaction and expression. (98)

Focusing on the communication style in online discussion groups, there are a lot of different results depending on the study. Glasgow Caledonian University examined 197 introductory psychology students and show that significant gender differences were found in the use of many stylistic variables and interaction styles. Males were more likely to use authoritative language, using assertions, presuppositions and judging opinions, compared to females,

which were more likely to agree and support others. Also, females use more intensifiers such as “really” and “totally” in their postings, than males do. One of the aspects to highlight is that females made contributions in a more empathic way, containing personal experiences, emotions, and their own feelings, posting messages that are more attenuated. This may be related to findings from another study that show gender differences in the topic of interest, where females tend to talk more about their private lives, such as family, friends and that’s why their language is more likely personal, while men tend to talk about public lives, such as government and public figures. This is related to what it was said before in this document and previous research where women tend to use the internet as a communication tool while men use it as an information seeking tool. [97] [98] [99] [100]

Another variable of study is the Internet habit strength which has been found to be positively associated with online communication, with the characteristic of being stronger for females than for males. In other words, females with stronger internet habit strength tend to engage in online communication more than males do. However, there is still a gap in this association because research findings are inconsistent across different studies. [101]

A.6.2 Gender differences in online shopping

Online shopping is becoming one of the most popular consumption choices accompanied by the emergence of e-businesses that have changed people’s social lifestyle point of view. The substantial growth of this type of purchasing has created great interest in understanding what impact people’s decision to buy or not online. In fact, there are studies that investigate the impact of online communication on online purchase and the gender variation on this impact. Consequently, a better understanding of online shopping attitude is critical to help business create and design effective websites that attract online customers. Gender difference in online shopping have been studied from different perspectives such as perceived risk of buying online, website usability and design, technology acceptance and attitude. [102]

Results have shown that the direction of attitude when shopping, is different between genders, where males often are goal-oriented shoppers motivated by convenience and females tend to be interest-driven and motivated by emotional and social interaction. It has also been found that communication does impact on online purchasing with more effect on women than men, but both had a positive effect. In this way, providing an online communication platform in an e-business website, can allow to social attributes and increase consumer behavior. [95] [102]

Moreover, three attitudinal components: cognition, affect and behavior; were examined through a survey of 80 students enrolled in an electronic commerce course. Results showed significant gender differences across the three attitudinal components. In general, women’s cognitive, affective and behavioral online shopping attitudes are lower than men’s, being cognition the lowest. Cognition of an object plays an important role in affect and behavioral intention towards that object. Thereby, women’s low cognitive attitude may explain the low

affection and behavioral attitude toward online shopping. Being that cognition refers to the evaluation of pros and cons of an object, this finding suggest that females are not sure about the benefits and risks of online shopping. In this way, business should focus on increasing women's awareness of the advantages associated with online shopping. Also, enhancing website design and making it more attractive improves the affective feelings and attitude towards online purchasing. [102]

Research has also focused on examining gender differences in perceived risk of buying online and the effects of the word of mouth and recommendation of a friend. Following this line, results has shown that women are more concerned about the security and the perceived risks of buying online than men, even if they are experts in Internet usage. However, it has also been found that a recommendation of a friend has a greater effect on female's intention to buy online than it has for a male's, which results in a significant reduction in the perceived risk among women. [103] [104]

Another study that examined the gender differences regarding the influence of inconsistent reviews on the internet, showed that females are more responsive to a mix of positive and negative reviews. As a consequent, females tend to shop more online in such circumstance than males, suggesting the idea of females considered as comprehensive information processors and males as selective information processors. [96]

A.6.3 Gender differences in social networking sites

Social Networking sites supply a place for individuals to interact and stay in touch with other people, and are becoming a crucial part of everyday life. [105] [106]

These websites have communication features that enable people to send instant messages, post photographs and messages, use the blog, send private messages, create groups, or play games, etc. [105]

Language and communication through electronic sources such as emails, Facebook, and other social networking sites is being a subject of current study by a lot of researchers, especially in terms of gender differences. Examining how women and men react and accommodate to gender-preferential language in social networking sites is very important and have aroused great interest. Results from different studies have shown that more intensive adverbs, personal information, subordinating sentences, modals and compliments are used when writing to a female style-language user that is labeled with a female name, compared to a male style- language user labeled with a male name. On the other hand, more insults, opinions and adjectives were used when writing to a male style-language user. This suggests that, no matter what gender one person is, language style is changed according to which person you are writing to. However, another experiment was done with 33 females and 32 males communicating with users where their name label didn't necessarily match to the style-language they were using. (eg. A user called Laura using a male-style language). Results here

showed that participant's language was a consequence of both their own gender and the gender language-style from the user. Also, but with less influence, gender label had some effect on the participant's style-language. This suggests that although an individual's own gender affects to the communication style, the gender and style of the partner who you are communicating with, has a greater effect to use a gender-preferential language in electronic messages. (44) (99)

The social context theory states that people tend to behave following stereotypes in front of a large and unfamiliar group, whereas in private communication this stereotyping behavior is reduced. In this way, public replies to Facebook status updates could be considered as a large and unfamiliar group communication; and private messages, as a one-to-one conversation with someone familiar. Gender differences in terms of public replies to Facebook status updates showed that females tend to reply more than males and using a more emotionally manner with a high level of support. However, these differences between males and females are not seen in private messages, supporting the social context theory, where in private, people behave less stereotypically and gender differences are reduced. (106) Another study also showed that Facebook users introduce themselves online in a less gender-stereotypical way compared to off-line contexts, and that this was seen more in women than in men. (107)

It has been stated before that social media is used by the people as a network to connect and maintain social contacts, reflect their daily routines and activities, share information, discuss topics, etc. As this type of online communication is becoming more popular, an increase in women using these technologies is shown. In terms of Internet use and spent time online, women tend to be more socially users, interacting and connecting with others, and maintaining relationships, while men are more task-oriented users, focusing on gathering information and activities such as reading the news. In line with the fact that women use social networking sites to maintain relationships and connect with people, online video calls have also become one of the tools with a greater use in women than men. Regarding the overall use of social networking sites, the number of males and females that are Facebook users is variable depending on the study, so results are inconsistent. Additionally, it has been seen that men tend to use social networking sites for dating, meeting new people, learn about events, find job leads and make friends. Women, moreover, use these sites for posting pictures, comments and send messages; although they care more about their privacy and that's why they interact with people they already know and trust. (105) (108)

Emailing is another way of online communication which women are more likely to use with their family and friends, than men. In addition, a lot of women have said that emailing has a significant role in their lives. On the other hand, men tend to use the email to collect information. (108)

Gender has also been found to influence in information diffusion within social networks. It seems that men tend to receive a given message that could influence in social mobilization, more than women do. (109)

Social media can also be a dangerous tool for adolescents in terms of online aggression or online bullying. In this way, there is also a gendered behavior which places adolescent girls to be more related to online bullying while boys are located in off-line face-to-face bullying. (110)

Regarding the profile picture, there has also been found gender differences. Women change more regularly their profile pages and give less personal information than men do. In fact, men are riskier with their photographs or information. (105) Also, compared to females, males tend more to have a profile picture of themselves alone. The male's motivations when choosing the profile picture are to look attractive, show how they are having fun and share unique moments. Also, men tend to show their status (wearing formal clothes or using objects). Female motivations are to look attractive, show how they are having fun, present special moments, but also protect their privacy, exhibit their interests and show their family relationships and emotions by smiling or giving eye contact without sunglasses. These results from different studies suggest the idea that, women are more diverse than men and that not only women think about showing their attractiveness, contrary to what Manago, Graham, Greenfield and Salimkhan investigated. (111) (112)

Social media use can differentiate between high frequency users or low frequency users. When studying gender differences in this field, more high frequency users tend to be woman compared to the low frequency users, suggesting again, the women tendency of using social media to stay in touch and maintain their relationships. (113)

Instagram is another social networking site consisting on photo-sharing that has become nearly the most popular in the last 5 years. The main characteristic of this social network is the "hashtag". Hashtags are non-spaced words, sentences or expressions following the sign # that allow users to look for their interests, describe their pictures and gain visibility online. Gender differences are being studied to see how men and women use these hashtags. Research has found that in line with prior studies about gender attitude in computer-mediated communication, females tend to use more emotional and positive hashtags while men use more informative hashtags. (114)

Regarding instant messaging, some studies have shown that females tend to be more "talkative" with longer conversations, spending more time saying goodbye and using a larger number of emoticons, compared to males. (99)

A.6.4 Gender differences in smartphone and texting

Young generations have grown up with cell phone access and has become an essential part of their lives, spending a considerable time texting or calling. Gender differences in this way of communication is also being studied by a lot of researchers. (115)

Smartphones are the new versions of mobile phones that have become very popular. They have millions of users and they offer a huge variety of applications (enjoyment, social, pastime, photography, etc.). Researchers are studying the risks of smartphone addiction and

whether these are different across genders. Some results have shown that female users are more likely to develop smartphone addiction by the effects of entertainment and pastime, while males tend to addict to smartphones by the effects of conformity, to avoid disapproval among their friends. (116)

Mobile phone usage can cause disruptions when driving or walking, learning in class, or during a face-to-face relationship. It has been found that females tend to spend more time using the mobile-phone to speak with their friends and family. Men, on the contrary, use them in a more informative way. Texting has also been found to be more used by women than men, especially to maintain their social interactions. It seems that this new way of communication by texting is eclipsing calling. (115)

Regarding the etiquette of cell phone use there are different beliefs between males and females. Overall, people think that texting is more acceptable than receiving or giving calls in a lot of different situations (public, intimate, interpersonal), except when driving. Regarding gender differences, men think that calls are more appropriate than women in all different situations, but for texting, men believed it is more appropriate than women only in public social situations. In other situations, no significant gender differences are found. Also, it is more likely within younger groups that females are more likely to text and call their mothers and fathers, than men do. (115)

A.6.5 Gender differences in eye tracking

Eye movement when reading a document is being a recent object of study for investigators that allow to map cognitive activities and provide information to improve effectiveness and efficiency on comprehension, science education, etc. (117)

Eye tracking is a technique used to follow eye movements and study the internal cognitive processes related to it. There are different variables used in the study of eye tracking such as location of fixation, gaze duration, regression (look back), pupil size, etc. Differences in location of fixation means differences of attention. Different gaze duration is related to the level of processing, being a deeper processing associated to a longer gaze duration. Regression is related to the working memory capacity and the reevaluation of the information already processed; and pupil size is related to the level of concentration. This technique is normally used in the fields of science education in order to provide teachers efficient ways of teaching their students, gaining knowledge about their cognitive abilities, but of course, it can be used to study many different fields. (117) (118)

Eye tracking can also be used as a tool to study user behavior during online search, specifically to understand activities such as reading, scanning, processing of visual stimuli and cognitive load. There is great interest to find whether men and women have different preferences when viewing information either on a website or a paper document, or during online searching and how eye tracking can study these differences. (119)

Fixations are motionless gaze of 200-300 milliseconds where visual attention focus on a specific area and it has been related to intense cognitive processing ability. Saccades are rapid eye movements that last 40-50 milliseconds where almost no information is captured. Pupil diameter, gaze duration and number of fixations are metrics used to measure user engagement and mental processing. In this way, it has been shown that fixation frequency in a repeatedly area displays degree of importance and mean gaze duration shows complexity and task difficulty. Larger pupil size is related to cognitive load and concentration when viewing some components of a web-page in an online context. One research conducted with majors in communication focused on the study of ocular behavior on web pages using eye movement metrics. The websites chosen were categorized in 4 types: shopping, business, search and news, and the procedure selected 2 pages from each website; the home page and a specific page related to the website (e.g. If it's a news website, a news article.) Results showed that, generally, females had shorter mean gaze duration than males and that the first pages of the websites had longer gaze duration than second pages, suggesting that males do more cognitive effort and deeper processing and that first pages need more cognitive effort than second pages. [119] [120]

Regarding online search tools such as Google, another study concluded that scanning patterns of the results page is more linear to males than females. In this way, females were more likely to make regressions and go back to already visited abstracts. [119]

Another study conducted in Spain to examine eye tracking when reading online news found that, when viewing the home page, females tend to read in a vertical manner while males read in a zigzag manner. [121]

Gender differences in attentional behavior considering text information or picture stimuli when looking at a website has also been studied using eye tracking. One study conducted with 120 subjects (60 women and 60 men) showed that, for the first ten seconds, the density distribution was clearly different between males and females. Women tend to focus on textual information more carefully while men pay more attention to photos or pictures, and they read less. This is supported by another study that stated that for male students it should be better to give graphical and picture explanations before the main text, while for females, it is better to give verbal explanations before graphics and pictures. [117] [122]

Another study that scanned eye tracking in virtual navigation and orientation, showed that females tend to have longer fixations on the virtual environment and larger pupil diameter, which is associated to memory processing, while men tend to look to more space with shorter fixations and less pupil diameter. [123]

Science performance and science problems solving have also been studied by different researchers through eye tracking to find gender differences. Overall, previous studies found no significant gender differences in science performance under untimed conditions. However, under timed conditions, science performance varies between males and females, being the

last ones at a disadvantage. In this way, females spent more time to solve a science-problem because they pay more attention to details and are more accurate. Men, on the other hand, focus on speed and solve the tasks more rapidly. Spatial working memory capacity of an individual influences in their science performance and has two components: phonological and visuospatial storage. The phonological is related to the temporary storage and process of verbal information while the visuospatial is related to the temporary storage and process of visual information. In this way, previous studies have shown that males have better visuospatial capacity than females, meaning that males have better skills to understand and memorize diagrammatic information in science, without the need to go back and make regressions to the diagrams. Eye tracking results from a study with students in Taiwan have shown that females have longer gaze duration and more fixation counts than males in textual information. While males tended to read only key pieces of the information provided by the diagram without reading it all, so in consequence, their gaze durations were shorter and fixations counts were less. [(118)]

A.7. THE PATIENT - PHYSICIAN COMMUNICATION

A.7.1 Why is important?

The communication physician-patient is essential to create a favourable environment to talk about different health topics, including the health research and the proper explanation of the informed consent.

Several authors address the issue of communication in the clinical practice and/or the need of improving the communication skills of the physicians; for example:

- Turabian, Minier-Rodriguez, Moreno-Ruiz et al. say that *"communication is an important component of patient care, maybe the most important aspect of practice that health care professionals have to master. The physician-patient interview is the key component of all health care, particularly of primary medical care"*. They also indicate that good communication skills by the physician have been connected with positive outcomes (as patient and physician satisfaction or better levels of adherence to therapeutic recommendations). [47]
- Ha and Longnecker highlight its importance indicating that *"doctors with better communication and interpersonal skills are able to detect problems earlier, can prevent medical crises and expensive intervention, and provide better support to their patients"*. [124]
- Huang, Huang, Yang et al. also point out that the establishment of rapport between patient and physicians contributes to the patient's satisfaction while a bad communication is a predictor of patient complaints, and they recommend that other countries follow the example of UK that requires to all they medical schools to examine the competence of the students in clinical communication. [125]
- Ahmed and Bates [126] highlight the importance of and effective communication to improve health outcomes, as patient satisfaction; and they consider that an effective communication is *"patient-centered, informative and that promotes trust and confidence*".

Other authors indicate its importance in the field of informed consent and/or clinical research; for example:

- Bento, Hardy and Osis indicate that Informed Consent is not only the signature of the form, and "*it is a process that begins at the first point of contact between the investigator and the potential volunteer and which continues throughout the study. This process consists of the investigator supplying information relating to the study, answering any questions and ascertaining that the person has understood the information he/she has been provided with, and allowing the volunteer, if he/she wishes, time to consult with other people" [127];* so improving communication between potential participants and physicians is of great importance. They also highlight the

important of a proper communication because if the participant doesn't understand the information well he/she won't be able to make an autonomous decision.

- Nishimura, Carey, Erwin et al. [128], after a systematic review of 54 interventions and meta-analysis of 22 interventions, point out that the best way to improve comprehension of the IC is enhanced consent forms and an extended conversation between investigator and participant; and they emphasize the importance of improving communication skills.
- Hayman, Taylor, Peart et al. [129] found that most useful information identified by parents who were invited to enrol their baby in a research project was the researcher's verbal explanation, a long distance from other sources of information as the written information sheet or the pamphlet, and they indicated that some studies highlight the positive effect that has an adequately information with the decision of participate in research for altruistic reasons.
- Stevens and Pletsch [130] also indicate that the relationship between the patient and the health care professionals has a lot of influence in the decision to participate or not, even more than what can be written in the IC.

Ha and Longnecker [124] identify the 3 main goals of physician-patient communication, which are: to generate a good interpersonal relationship; to smooth an exchange of information and; to include the patient in decision making. They also indicate that most complains that physicians receive are not because their clinical competency but because of issues of communication.

A.7.2 Gender differences in the relationship physician-patient

As Acuña [2] and Cameron [37] point out, and has already been said in the section *A3.2.4 "Diversity, constructivist and performative approaches"*, the focus nowadays instead of been in the differences about men and women must be in the context and the type of men and women; so in this point the gender differences try to focus in the *"type of men and women"* (patients and physicians of both genders) and in a context (usually clinical conversations), but even in this case the differences are about styles and are not categorical.

Street [131] analyses the communication in medical encounters through the ecological perspective, and highlights the impact that contexts (media context, cultural-socioeconomic context, political-legal context, organizational context and interpersonal context) may have on the medical encounter. And explains that ecological model identifies two different sources of adaptive behaviour: the cognitive-affective factors (for adaptation based on strategic, attributional and relational considerations) and the partner's communicative actions. He also points out that several factors such as personality, identity, socialization and linguistic styles have been associated with communication differences; and, in the case of physicians-patient communication, a complex interaction of style, perception and adaptation must be taken into account. He suggests that gender differences in communication between patient and

physicians can be explained by factors as gender communication differences in other contexts; gender-based perceptions, attitudes, expectations and beliefs or; the partner's communicative actions. Even so, he indicates that males and females physicians still have more similarities communicating than differences and that gender differences in communication are usually more evident among physicians than among patients.

Hall and Roter [71] indicate that there are gender differences in communication between physician and patient, some of them due to the way physicians communicate and others because of the way patients treat the physician according to their gender. They indicate that the differences mainly correspond with the gender differences in communication by non-clinical population. Just as women are often more emotionally expressive, tend to have more positive and engaged non-verbal behaviors (such as smiling, nodding, and looking at a partner in conversation), and usually are more egalitarian in interpersonal relationships, female physicians tend to communicate with behaviors usually associated with positive effects to the patient; in fact it has been suggested that female physicians create a therapeutic milieu more favorable than male physicians. As example of the differences in characteristics of gendered communication in non-clinical population that also appear in clinical population, we can use the assessment that Holmes [69] does when she indicates that male physicians use more imperatives (e.g. *"eat more fruit"),* while female physicians use less direct forms (e.g. *"maybe you could try fresh fruit for dessert*").

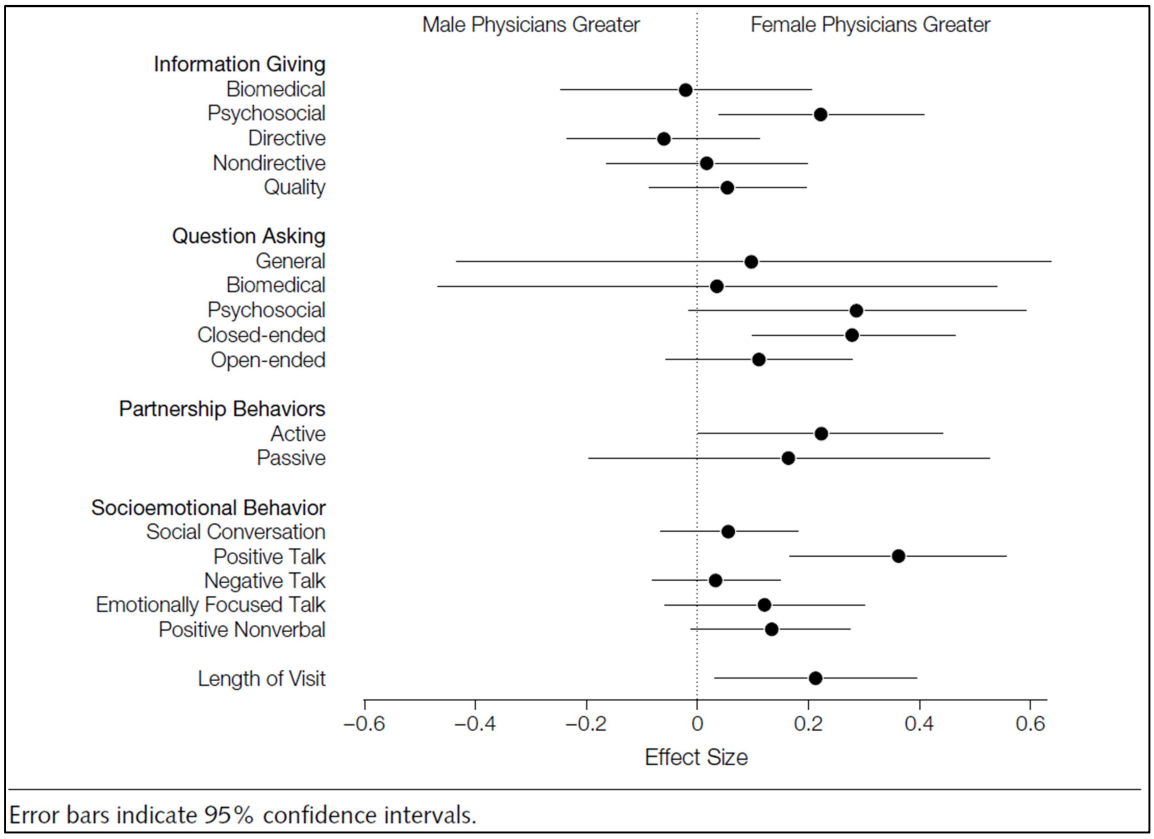
A.7.2.1 Physicians communication

Bertakis, Helms, Callahan et al. [132] point out that there are gender differences in the way physicians communicate to their patients, indicating that female physicians engage in more positive conversations, build partnerships, ask more, and provide more information; and patients evaluate these attitude as positive, evaluating the experience as more satisfactory; this is more evident if the patient is a woman, in fact some studies indicate that female patients use to prefer to be attended by female physicians while male patients use to prefer to be attended by male physicians. In their research done with 250 new patients (118 males, 132 females) and 81 medical residents (48 male and 33 female) in California (USA) they found that female physicians spend more time discussing about the patient's family (medical and social matters, and current family functioning) and social context while men physicians spend more time with the history taking; they also registered a biggest satisfaction with the female physicians, but this can be in part explain because of the differences in the practice style, as patients usually feel less satisfy when the visit is very focused on history taking. So they suggest the importance of identifying the behaviors that are associated with a better patient's satisfaction and teach them to medical students.

Roter, Hall and Aoki [133] did a systematic review of the literature and a meta-analysis to quantify the effect of the gender of the physicians on their communication with the patient during the medical visit, they considered 26 studies (23 observational studies and 3 large physician-report studies) described in 29 publications. They synthetize their findings as

"female physicians engage in significantly more active partnership behaviors, positive talk, psychological counseling, psychosocial question asking, and emotionally focus talk. There were no gender differences evident in the amount, quality, or manner of biomedical information giving or social conversation. Medical visits with female physicians are, on average, 2 minutes (10%) longer than those with male physicians" (figure A.1 show the results graphically).

Figure A.1. Estimated pooled gender effect sizes for categories of patient-physician communication in the meta-analyses done by Roter, Hall and Aoki.



Source: taken from "Physician gender effects in medical communication: a meta-analytic review" [133]

They also conclude that female primary care physicians tend to use a style of communication more centered in the patient; they also point out that may exist differences in some patterns of communication between primary care physicians and some subspecialties (as obstetrics and gynecology). [133]

Hall and Roter [71] indicate that physicians communicate differently to male and female patients; generally they tend to become more involve with female patients. Physicians usually communicate more, give more information, build more partnership, direct more positive talk, emotionally concerned statements and disagreements with female than with male patients.

A.7.2.2 Patient communication

Turabian, Minier-Rodriguez, Moreno-Ruiz et al. [47] indicate that there are three groups of conditionings that influence in patients participation in medical interaction:

- The personal characteristics of the patient, as age, gender, ethnicity or education.
- The communication style of the physician as question asking, use of partnership-building or supportive talk.
- The clinical setting as the health condition or the medical specialty.

They did a study analyzing twenty consultations done by a male physician with eight male and twelve female patients, and found very small gender differences in communication, being only remarkable that interviews with women they (the patient women) were more supporting and registered less disagreement. [47]

Hall and Roter [71] did a meta-analytic review about how physician gender affects the patient communication in medical visits; they expected to find that, in general, patients treat the physicians as they treat them, following the reciprocity principle. The results they found are quite consistent between most of the studies, except with one or two studies on obstetricians-gynecologists that were removed in some analyses. The main results are:

- Patients talk more and give more biomedical and psychosocial information to female physicians.
- Patients promote more a partnership relationship with female physicians.
- Patient positive talk (including statements of agreement) is more common toward female physicians.
- Patients direct more anger or irritation toward male physicians (only one research studied the anger or irritation)
- Patients are more assertive with female physicians.
- There are non-significant differences in the amount of questions that patient ask by physician's gender; neither in social conversation (non-medical chitchat); patient negative talk (including disagreements); patient emotional talk (which included statements of concern, worry, and personal feelings); tendency of the patients to display more positive affect (as friendly, warm, kind) or to speak with anxiety to the physicians.

The principle of reciprocity is fulfilled in the greater tendency of the patients to have positive talk, give psychosocial information and build a partnership with female physicians. In the case of the biomedical information, may be patients give more information to female physicians because they use to ask more questions or because they do more efforts building a partnership.

In general it seems that patients feel more comfortable, committed, communicative, and assertive when talking to a female physician, what suggest that they feel more empowered. The evidences analyzed in this research show that it exist differences in the tone and content of the medical visit depending on the physician's gender.

Another observation that the authors do is that male and female patients communicate in different way. Feminine patients tend to have more emotionally concerned statements,

disagreements, and positive statements, and they usually do more questions to physicians than male patients.

A.7.2.3 Gender concordance and communication

Roter and Hall [134] point out that some gender effects in communication between physician-patient in medical visits are stronger in same-gender dyads than in mixed-sex ones. They note that:

- Female dyads physician-patient are characterized by longest encounters and most equal contributions from both (patient and physician) to medical dialogue, with higher levels of psychosocial discussion, emotional exchange, and eye contact; and have lesser levels of physician verbal dominance. They also present more positive statements, head nodding, and interest cues than the rest of combinations.
- Male dyads physician-patient are characterized by shortest visit time and the highest level of physician verbal dominance.
- These differences appear to be consistent in most of the countries.

A.7.2.4 Accommodation in physician-patient communication

Communications between physician and patient has been seen as an unbalance relationship, where usually physicians have the power and the patients are the weak part, sometimes this power imbalance have brought situations where physician use a very clinical and complicated language for the patients, have dominating attitude or aloofness, causing in the patient a sensation of unsatisfaction. Physicians may accommodate their communication style to balance these relationship and increase patient's satisfaction.

A research done by Watson and Gallois [38] with 134 participants that rated 16 descriptions of conversations on 13 items derived from the CAT, they identified the items that had higher rating in satisfying conversations than in unsatisfying; the first important conclusion is that they didn't find significant differences in the score given to the items, neither in the consideration of the conversation as satisfactory or unsatisfactory by gender. The items that were significantly better scored in satisfactory conversations than in unsatisfactory one, divided by areas, are:

- Discourse management:
  - "Treats patient as individual".
  - "Listen to patient's needs".
  - "Takes patient's views into account".
  - "Patient chooses topic".
- Emotional expression:
  - "Reassures patient".
  - "Show concern for patient".
- Interpersonal control:

- "Patient has control".

- Assessment of behaviour:
  - "Typical health professional".
  - "Health professional's behaviour appropriate".
- Outcome
  - "Pleasant conversation for patient".

While the ones better scored in the unsatisfactory conversations than in the satisfactory ones were:

- Interpersonal control:
  - "Talks down to patient".
  - "Health professional controls conversation".

These show that participants think that patient should be taken into account and to also have an important role in the conversation, for example participating in the topic selection, and their relationship and emotional needs also have to be attended; but health professional still have to maintain his/her typical role, and the control has to be well balance, in fact, the over-control is seen as negative for communication.

In a more recent research, Ahmed and Bates [126] indicate that the literature strongly recommends the physicians to accommodate towards patients and discourage the divergent communication. In their study with 310 patients they analysed the impact of different CAT strategies by the physician (taken from Watson and Gallois [135]) to the satisfaction of the patient. They realise that, in general, convergent communication improve the satisfaction of the patient, but not always, and depending on the different goals and areas, an accommodation strategy will be recommended:

- In the area of discourse management, that pursue to treat the patient as an individual, patients mostly prefer physicians to use the convergence in all four CAT strategies ("Treating the patient as an equal"; "Maintaining a good relationship with the patient"; "Treating the patient as an individual"; "Asking questions of the patient") being more satisfied when the physician use this strategies.
- In the area of emotional expression, that seeks to understand and respond to the patient's socio-emotional needs, patients prefer physicians who converge by "Reassuring the patient" and "Reducing the patient's anxiety". But for the third strategy "Showing liking for the patient" they prefer the ones that do it always or never, but not the ones who do it moderately.
- In the area of interpretability, with the objective of understand and respond to the informational needs of the patient; patients prefer physicians who convergence with the strategies of "expressing himself/herself clearly to the patient", "checking to see if the patient understands" and in a lesser extent "looking comfortable with the patient" (in this last strategy, few patients prefer physicians to don't use it). With the strategy

"Handling conversation competently", patients prefer the physicians that always or never converge, more than the ones who do it moderately.

- In the area of interpersonal control, whose aim is to establish authority, expertise, and power in the clinical interaction. Patient prefer when physician controls the conversation (perform strategies of "Controlling conversation"; "Deciding on topics talked about"; "Talking down to patient"; "Intruding on patients' privacy") followed by the ones who cede control to the patient, but the most unsatisfied attitude is when the patient doesn't know if the physician controls or cede the control over the conversation.

It seems that patients expect that the physician control the conversation, but they still want to keep their autonomy, be well informed and understand the content of the conversation (but using a proper language for the consultation). Ahmed and Bates also indicate that patients may perceive that the physician is not interested in their case or misunderstand their necessity of information if they perceive that they don't converge at all; but they may feel that the physician are patronizing instead of making an effort to find common ground with the patient if they *"overconverged"* and use an everyday language in the consultation. [126]

A.8. WOMEN'S OPINIONS ABOUT THE INFORMED CONSENT PROCESS

This section summarises the research done by Bento, Hardy and Osis concerning to women's opinion about the informed consent process [127] because:

1. with its qualitative methodology brings the information about the women's thoughts, their opinion, perceptions and feelings without suggested or close answers and allows to discuss in deep about each topic;
2. we didn't find any other study with these characteristics and so specific about the topic of the deliverable;
3. even it only presents the women's point of view, without comparing it with that of men, we consider it adjust perfectly to the objective of the document since the actual way of doing the inform consent process is predominantly masculine, as Lasarte says *"when we speak of gender we speak of the feminine, since the masculine is invisible and universal of pure omnipresent"* [81].

Bento, Hardy and Osis [127] did a research analysing the opinion of women about the informed consent process in studies about contraceptive methods. They did eight focus groups and counted with the participation of 51 women, with ages between 18-49 years old, who were participating in a clinical trial in the area of women's health or had participated in the last 12 months and who lived in the metropolitan area of Campinas, Sao Paolo (Brazil), the date isn't specified but the article was published on 2008. The topics that they studied and their main findings are:

Professional who should supply the information about the study:

The person who invites the women to participate:

- Should be a member of the research team but preferably not the principal investigator, better if is not a physician and should have knowledge of the study, appear secure and been able to answer the questions.
- Will be the reference person during all the research, their link with the project, the one the women will look for advise, should be someone accessible, always available to give the guide the women may require about what to do and when to do it. *"This relationship should result in a real friendship that offers a greater sense of security to the study volunteers"*.

The authors indicate that, as the physician-patient relationship has been socially marked as a relation of power and physicians are considered to belong to an elite social and cultural class, some people may feel intimidate and feel inhibited to ask questions or questioning what the physician says, affecting their understanding and limiting their autonomy; and even if the researcher is not a physician there is always an unbalanced relationship were the volunteer is seen in a weak position.

Attitude of the professional

- Women indicate that the decision to participate or not will be influenced by the attitude of the professional, and they point out that when he/she has an arrogant attitude they feel as if they are "objects" or "laboratory rats", while if he/she is attentive and accessible they feel more receptive to talk about the invitation and more comfortable to ask questions.

Is important to remark that women put the accent in aspects like politeness, accessibility, receptiveness instead of in aspects related to technical competence. Bento, Hardy and Osis indicate that Boltansky concurs in the same idea indicating that when people can't evaluate the technical competence of a physician they focus in his/her attitude, such as if is polite, patient, well-disposed or pleasant.

The way in which the information is given

Women indicate that:

- They would like to receive the information in groups of around 10 women and also individually (both, one complements the other). Indicating that to do it in group facilitates the exchange of information between them, while does it individually give them more freedom to ask or do comments that they can feel embarrass to do in a group. Some indicate that only with the information in group would be enough, because as all of them are women they won't feel ashamed to do any comment or question.
- The information should be given in written and orally format (complementary). Oral format favours an exchange of ideas and asking questions that give more security, but is important to do it as long as necessary and to feel that the woman has understood all the information given and has everything clear. Written informed consent form should include all the information given orally and is important to give it to the woman so she can access to the information again if she wants.

The authors explain that there are evidences about the improvement in the understanding in collective explanation versus individual, which may be caused because the information provider could use more time and use audio-visual aids. They also highlight the importance of give the time necessary to give and discuss the information.

Information that they would like to receive

- Women consider that to been able to decide about participating or not they should have information about risks and benefits, efficacy and possible side effects and inconveniences (short, medium and long term ones).

Quantity of information

- Women don't specify which amount of information they consider enough, the important thing for them is to have the information clear. They give more importance to the manner the information is provided (clearly and objectively to be easy understanding) than to the quantity. But they also point out that to have a lot of information to read may be counterproductive, because people usually don't have patience to read a lot of information, and it can be discouraging if the woman has difficulties to understand the information (what has to be especially considered in developing countries or in the ones with significant proportion of women with rudimentary reading skills).
- Some women prefer that the person providing the information reads it out to them while others prefer to read it themselves because it helps them to think more clearly.

There is an important controversy about this topic, because the principilist theory highlights the important of giving all the information to the potential participant to preserve the principle of autonomy, but usually it ends up in long ICF with detailed information about the study. Extensive ICF may be as prejudicial as to give little information, because both situations have the risk to reduce the emphasis on the relevant information to take an autonomous decision about participating.

Even so, we want to highlight the ending sentence that the authors use about this section in their article: *"There is evidence that volunteers decide whether to participate in a study before they read the consent form, after receiving oral instructions"*.

Teaching aids that may be used

- Women point out that audio-visuals (videos, posters, leaflets…) could contribute to improve the understanding and it can be specially appropriate to show in the film the procedures they will be submitted if they accept to participate if proceeds (is important to take into account that the study was about contraceptive). They also appreciate if contraceptive method and statements from women that are already using it are shown.
- They also consider useful to have some materials to take home, such as slides or information recorder on a cd/dvd/usb can be useful, so they can use it or share it with other women.

The authors indicate that other studies didn't find evidences about how use of audio-visuals improve understanding, but they point out other benefits of using them, such as that they contribute to a better retention of information or to assure that same information is provided to all potential participants.

As final remarks Bento, Hardy and Osis indicate that women don't consider the process of IC as a ritual mainly represented by the signature of the form and they understand it as a link between the potential volunteer and the investigator.

Other contributions

Stevens and Pletsch [130] indicate that *"informed consent must be explained and obtained in a gender-specific and culturally competent manner"*, and they highlight the importance of taking into account factors that within the gender have impact on social context and health, as the ethnicity, class or country of birth. They also state the convenience of tailoring the IC to make it consistent with the beliefs, values and preferences of the potential participants.

A.9. CONCLUSIONS

A.9.1 About gender differences in communication

Gender differences in communication is a very controversial topic that has progressed from some studies and position that defend the existence of clear differences and presents women's language as inferior to that of men's, until approaches more extended nowadays that defend that there exist some differences between gendered styles, that are not assigned to one fixed gender and people can change from one to another depending on different situations(not all women must use the style typically assigned to them, and neither all the time, they can change from different styles, ones more feminine and others more masculine). Gender is considered only one of several conditionings of communicative activities and that understands that men and women are heterogeneous groups, where differences among them may be even bigger than the ones between genders.

Gender stereotypes seem to have an effect on the way men and women communicate, and the characteristics that have been associated with the masculine and feminine style enhance the development of the abilities and personalities that allow them to fulfill the roles assigned to each one of them by society, what Lasarte [(81)] calls the ethic of power -attributed to men- and the ethics of care -attributed to women-. These characteristics are, for example: security, dominance, competitive, person distant or oriented to professional and public development in the masculine style; and tentative, caring, polite, person close or oriented to care, housekeeping and private development in the feminine style. There exist also gender differences in the understanding of some communicative actions, such as minimal responses.

The way men and women communicate in same-sex and mixed-sex dyads or groups also differs and the "Communication Accommodation Theory" explain some of these differences, that are related to the modification of the communicative behaviour depending on the characteristics of the partner and the personal goals.

Even so, a lot of authors highlight that men and women have more common characteristics than differences; and the differences found are not categorical.

A.9.2 About gender differences in skills

Most of the studies in this field are done to scholar population and based in the stereotypes and hold that males are better in mathematics and spatial tests, and females on verbal tests. The studies also indicate that usually girls are more motivated than boys to read and are better when deal with routinely tasks, while boys feel less anxiety toward mathematics and are more able to resolve problems "thinking like scientists". When they arrive to adult ages, usually men have already improve their reading skills to the same level than women, but they still better with mathematics and with the interpretation of graphic tasks. Even so, most of the differences in old ages become from the development of tasks at work, that nowadays and because of the labour gender differences (vertical and horizontal segregation on the basis

of sex in the labour market), give more opportunities to men to practice and improve their skills reading and solving scientific and mathematic problems, getting advantage in both fields.

A.9.3 About gender differences with ICTs

New technologies have significantly increased in the last decade and gender differences have always been a subject of study. The different ways in which women and men use Internet is the topic where a lot of researchers are focusing their investigations. Although results are inconsistent between different studies, what is clear is that, there is still an existing gap between females and males regarding online contexts. This review collects information about gender differences in different online contexts: online communication, online shopping, social networking sites and texting. Information regarding eye tracking results in online situations is also collected.

Overall, females tend to use online discussion groups as a communication tool with their families and friends making contributions in a more empathic way, containing personal experiences and emotions. They are more likely to agree and support others. On the other hand, men tend to use an authoritative language in online discussion and judging opinions with a less personal involvement, using Internet as an information seeking tool.

Regarding online shopping, males tend to have a goal-oriented attitude and are motivated by convenience whereas females are motivated by emotional and social interaction to buy online. Results have also shown that females are more aware than males about the perceived risks and benefits of buying online, even though they are Internet expert users, suggesting they need to be more encouraged to buy, for example, by a friend's recommendation, which has a greater effect in women than it has it in men. In addition, both genders are positively influenced by communication, meaning that when an online platform is present in an e-business website, consumer behavior increases.

Social Networking sites are also a platform where gender differences have appeared. In line with other online contexts, female users tend to reply public messages in social networks using a more emotional manner with a high level of support, compared to males. However, these differences are reduced when communicating by private messages, where gender-stereotypical language, decreases. Also, the uses of social networking sites differ between males and females. Males use them for dating, meet new people, gather information, find jobs… while females use them for posting pictures, comments, and communicate with their existing relationships. Moreover, online bullying is also more represented within adolescent girls, whereas boys are located on face-to-face bullying. Furthermore, profile picture is changed more regularly by women, being more diverse than men, and the hashtags also seem to be emotional and positive for women and informative for men, consistent with previous research and different contexts.

Texting has been found to be more used by women, especially to maintain their social relationships, and this way of communication is eclipsing calling. Also, men think that texting is more appropriate in public social situations than women do. No gender differences were found in thinking about being appropriate to text in private or interpersonal contexts.

Eye tracking has demonstrated different ocular movements between males and females when viewing a website, moving in a virtual environment, trying to solve a science problem or reading online news. These differences summarize in assumptions of females having shorter mean gaze duration than males when viewing a home page of a website, meaning that males do more cognitive effort. Also, females read the online news in a more vertical manner, whereas males tend to read in a zigzag way. Women tend to focus their attention in textual information while men pay more attention to photos and pictures. In this same line, diagram information is better understood by males, that have a better visuospatial capacity, when solving a science problem, with less regressions to the diagrams and shorter fixations, compared to females, that make more regressions and more fixation counts. Regarding virtual navigation and orientation, females tend to have longer fixations in the environment, paying attention to the details, while men look more to the environment in general with shorter fixations.

In conclusion, we are living in a technological world that is increasing very fast and although gender gap in online contexts has decreased significantly in the last decades, there will still be a gender attitude that comes intrinsically with the sex of the individual. Future steps should focus on trying to decrease this gap by offering tailored solutions to each gender, so both are in equal conditions within different online contexts.

A.9.4 About communication between physician and patient

The communication between physician and patient is a key issue in the relationship between them that has been related with better health outcomes and the patient's satisfaction. The need of increasing the physician's communicative skills has been suggested by several authors; being very importance to identify the aspects that can make the difference in interpersonal communication.

There are gender differences in communication between physician and patient, and they correspond mainly to general gender differences in communication, not being exclusive of the physician-patient relationship. Some of these differences are caused by how physicians communicate (his/her own gender and depending on patient's gender) and others because of the way patients communicate (his/her own gender and depending on physician's gender); in same-sex dyads some effects are stronger.

Some characteristics usually associated with female physicians have been evaluated by patients as positive and typical of a satisfactory experience. Usually physicians get more involved in communication with female patients.

Patients usually treat the physicians as they treat them, following the reciprocity principle; and they usually feel more comfortable, committed, communicative, and assertive when talking to a female physician. Patient's gender also influences their way to communicate.

Usually patients prefer the physician to accommodate their communicational behavior making the patient feel as an equal, taking him/her into account, taking interest on him/her, expressing clearly, reducing the patient's anxiety… but they also prefer the physician to continue having the control of the conversation and to don't "overconverge" using an everyday language.

A.9.5 About informed consent

Informed Consent process allows the subject to voluntarily decide his/her participation in a clinical trial. Generally, IC are documents difficult to read, that do not include all stakeholder's perceptions and do not distinguish between subject's characteristics, (age, gender, demographic characteristics, etc.)

Evidences show that IC forms are difficult to read [(88)] and its understanding hasn't improved in the last 30 years [(86)], hence the need to boost research in improving their understanding. In the present review, diverse analyses of factors that have influence in the comprehension of the IC have been found, as for example:

- The improvement of systematic lexico-syntactic readability improvement or the modification of the ICF by a working group, increase the comprehension in the phase I clinical trials. [(89)]
- To have more time to read the ICF, by taking it home, improve the understanding, especially for men. [(91)]
- The oral explanation by the physician, taking his/her time and adapting the language to the patient, is really appropriate to increase the understanding.
- Patients who used additional information sources and the ones who had at least 30 minutes for receiving information registered better perceived understanding. [(87)]
- Is more likely that people read the ICF complete in person than by remote access. [(92)]

Tam et al. didn't find significant differences to understanding informed consent in clinical trial by gender [(86)], only few studies point to differences and in most cases reflect and advantage in understanding, or even in the frequency to read the entire ICF [(92)], by women. Even so, is important to consider that we didn't find studies that analyse the gender differences in comprehension with ICF adapted to gender. The effect of how accommodation and adaptation by gender can affect understanding of the IC, especially by women, or the impact it may have on decision-making about participation in research, has never been studied and we think is a field that should be considered. Accommodation may also make IC form or process more attractive and increase the proportion of people who read the whole IC.

Even there is an important controversy about the convenience of doing a gender adaptation of the IC, Stevens and Pletsch [130] highlight the convenience of tailoring the IC to make it consistent with the gender of the participant, but also to his/her beliefs, values and preferences. This brings out the importance to consider the gender differences in communication and accentuates the need of continuing researching in this field.

Is important to remark the findings of some studies that identify the attitude or preferences of women around the IC process, for example Knepp found that women prefer to do the process face-to-face, are more caution to avoid manipulation and seek information more often than men [92]; or Bento, Hardy and Osis who did a research concerning to women's opinion about the informed consent process [127].

A.10. RECOMMENDATIONS FOR THE GENDER APPROACH IN IC

First of all, there are six important ideas that should be remarked:

1. The adaptation of the IC forms in format "paper" is very difficult and costly and the evidence doesn't show clear benefits that justify doing all this process (more research is need in this field) and we recommend to accommodate them for the moment only in cases that are addressed only to women. In other formats, as for example using the TICs or explained face to face this gender adaptation can be done easier.
2. The best way to improve the understanding of IC is to tailor it to the patient, having into account the gender, but also other determinants such as age or sociocultural level.
3. Gender differences in communication have been analyzed in this document. Gendered styles shown are useful, as tends, to guide the accommodation of the IC process to the patient's style; but never have to be taken as categorical.
4. Convergent accommodation has a positive influence in the perception of the observer and has been has been associated with a positive evaluation of the communication, the individual, and the relationship. [43] Accommodation may contribute to make the text more comprehensible, taking into account the characteristics of the potential participant, and to improve the strategy of recruiting participants in research, especially increasing the participation of women, avoiding an important source of gender bias (under-representation of women, mainly in clinical trials) and contributing to incorporate gender perspective into health research. But it should be done cautiously and "overconverge" should be avoided.
5. The process of Informed Consent starts from the initial contact between the research team and the potential participant till the end of the research. It covers the Informed Consent forms and any actions (supply information, asking questions…) that provides the potential participant with better understanding and respect of their dignity and autonomy.
6. More research is needed to be done in this field.

From our findings we can suggest the following recommendations to improve the informed consent process, especially within vulnerable population under a gender perspective:

- Is very important to take care of the format, do the form easily readable and take time to discuss it with the participants.
- Informed consent should include more graphics (noncomplex) and pictures, which facilitate the comprehension of the main text.
- Both genders have seen to have less anxiety and social pressure in online contexts, compared to face-to-face. In this way, it may be useful to create an online platform where subjects can ask questions and write their concerns to the research team, in addition to the face to face appointment, that is essential to encourage the complete read of the ICF and to increase the understanding.

- Consider the eye tracking behavior, working on the design and order of information on the informed consent so that the first look and read at the document is more efficient.
- Taking into consideration that women usually are more emotional, the researcher should focus on these emotional feelings when offering the informed consent. In this way, when a clinical trial has women as the only population recruitable (pregnant women, adolescent girls), the way of communicating should be done following emotional guidelines.
- Avoid mathematic concepts and complex graphics in the ICF addressed to feminine participants to avoid to produce anxiety.
- Do the IFC as short as possible using a direct and impersonal style, when oriented to men.
- Take into account the gender differences in the interaction as, for example, in the use of minimal responses, cooperative overlap, physical distance, visual contact, etc.
- Follow the considerations from the research of Bento, Hardy and Osis [127] about the women's opinion about the IC process (section A8 "women's opinions about the informed consent process"), taking into account that even women's preference is that the person who gives the informed consent won't be a physician, the European law indicates that the informed consent should be provided by a physician, so is important to consider the accommodation of language to break the distance between physician-volunteer. Other findings of that research were:
    - About the professional who should supply the information about the study: should have knowledge of the study, appear secure and been able to answer questions about the research; should be someone accessible, always available to give the guide the women may require about the research.
    - Attitude of the professional: attentive and accessible, avoiding arrogant attitude. Other studies remark that the characteristics usually attributed to female physicians have been identified as more positive and satisfactory, especially for women. So they should be taken into account and used as guide about how to behave.
    - The way in which the information is given: they prefer to receive the information in groups of women and individually (both complementary); and in written and orally format (also complementary). The conversation with the physician is very important and valued.
    - Information that they would like to receive: Women consider that to been able to decide about participating or not they should have information about risks and benefits, efficacy and possible side effects and inconveniences (short, medium and long term ones).
    - Quantity of information: They give more importance to the manner the information is provided (clearly and objectively to be easy understanding) than

to the quantity. But indicate that too much information could be counterproductive.

- Useful aids: audio-visuals (videos, posters, leaflets…) and some materials to take home, as slides or information recorder on a cd/dvd/usb. They contribute to a better retention of the information and to assure that same information is provided to all potential participants.

A.11. BILIOGRAPHY

1. European Commission. HORIZON 2020 - Work Programme 2016 - 2017 Science with and for Society. [Online].; 2016 [cited 2017 10 19. Available from: http://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-swfs_en.pdf.

2. Acuña V. Conversación juvenil e identidad de género: despliegues de feminidad heterosexual en grupos de jóvenes veinteañeras. Círculo de Lingüística Aplicada a la Comunicación. 2017;69:3-33.

3. Cameron D. Gender. In: Brown K, editor. Encyclopedia of Language & Linguistics (Second Edition). Oxford: Elsevier; 2006. 733-9 p.

4. Directorate-General for Research & Innovation. Guidance on Gender Equality in Horizon 2020 (version 2.0) Brussels: European Commission; 2016.

5. European Institute for Gender Equality (EIGE). Gender Equality Glossary and Thesaurus. [Online]. [cited 2017 July 18. Available from: http://eige.europa.eu/rdc/thesaurus.

6. García Calvente MdM, Jiménez Rodrigo ML, Martínez Morante E. Guía para incorporar la perspectiva de género a la investigación en salud. España: Escuela Andaluza de Salud Pública; 2010.

7. Guerrero S. Diferencias de género en evaluaciones de narraciones de experiencias personales en el habla juvenil de Santiago de Chile. Una aproximación sociolingüística. Revista Signos. 2011;44(75):18-32.

8. Prieto L, San Martín A. Diferencias de género en el empleo del discurso referido: aproximación sociolingüística y pragmático-discursiva. Boletín de Filología. 2002-2003; 39(1):269-303.

9. Thomason SG. Glossary. In: Brown K, editor. Encyclopedia of Language & Linguistics (Second Edition). Oxford: Elsevier; 2006.

10. Motschenbacher H. Can the term 'genderlect' be saved? A postmodernist re-definition. GENDER LANG. 2007;1(2):255-78.

11. Holmes J. Sex and language. In: Goebl H, Neide P, Stary Z, Wölck W, editors. Contact Linguistics: An International Handbook of Contemporary Research (Volume 1). Berlin: Walter de Gruyter; 1996. 720-5 p.

12. Hidalgo-Tenorio E. Genderlect. In: Naples N, Hoogland R, Wickramasinghe M, Wong A, editors. The Wiley-Blackwell Encyclopedia of Gender and Sexuality Studies. USA: Wiley-

Blackwell; 2016. 1–4 p.

13. Gregori A. Contra el generolecto: una lectura crítica desde el constructivismo. In Actas IV Congreso de Lingüística General. Santiago de Compostela. 2004. 3681-9 p.

14. Tusón A. Lenguaje, interacción y diferencia sexual. Enunciación. 2016;21(1):138-51.

15. Castellanos G. Los estilos de género y la tiranía del binarismo: de por qué necesitamos el concepto generolecto. Aljaba (Luján). 2016;20:69-88.

16. Poyatos F. Nonverbal Communication across Disciplines: Volume 1: Culture, sensory interaction, speech, conversation. Amsterdam/Philadelphia: John Benjamins Publishing Company; 2002.

17. Poyatos F. La Comunicación No Verbal como asignatura en Filologías Clásicas y Modernas. Didáctica. Lengua y Literatura. 2013;25:231-57.

18. Jespersen O. Language: Its Nature, Development and Origin. London: Allen and Unwin; 1922.

19. Torres Romo JJ. El constructivismo y las políticas del lenguaje: el habla de género. Revista Mexicana de Ciencias Agrícolas. 2015;2:347-55.

20. Lakoff R. Language and woman's place. Lang. Soc. 1973;2(1):45-80.

21. Uchida A. When "Difference" Is "Dominance": A Critique of the "Anti-Power-Based" Cultural Approach to Sex Differences. Lang. Soc. 1992;21(4):547-68.

22. Cameron D. On language and sexual politics. Oxon (UK): Routledge; 2006.

23. Maltz DN, Borker RA. A cultural approach to male-female miscommunication. In: Coates J, editor. Language and Gender. 1982. 417-34 p.

24. Zimmerman DH, West C. Sex Roles, Interruptions and Silences in Conversation. In: Thorne B, Henley N, editors. Language and Sex: Difference and Dominance. Rowley: Newbury House; 1975. 105–29 p.

25. Brown P. How and why are women more polite? Some evidence from a Mayan community. In: McConnell-Ginet S, Borker R, Furman N, editors. Women and Language in Literature and Society. New York: Praeger; 1980. 111–36 p.

26. Cameron D. Sex/Gender, Language and the New Biologism. Applied Linguistics. 2009;31(2):173–92.

27. Fishman P. Interaction: The Work Women Do. Soc Probl. 1978;25(4):397-406.

28. Gray J. Men Are from Mars, Women Are from Venus. New York: HyperCollins Publishers; 1992.

29. De Francisco VP, Palczewski CH. Gender in communication: a critical introduction. 2nd ed. USA: Sage Publications; 2014.

30. Mulac A. The gender-linked language effect: Do language differences really make a difference? In: Canary D, Dindia K, editors. Sex differences and similarities in communication: Critical essays and empirical investigations of sex and gender in interaction. Mahwah (New Jersey): Erlbaum; 1998. 127-55 p.

31. Tannen D. You Just Don't Understand: Women and Men in Conversation. London: Virago; 1990.

32. Talbot M. Gender and Language. In: Brown K, editor. Encyclopedia of Language & Linguistics. 2nd ed. Oxford: Elsevier; 2006. 740-2 p.

33. Alami M. Approaches to Gender Studies: A Review of Literature. Journal of Applied Linguistics and Language Research. 2016;3(3):247-56.

34. Mulac A, Bradac JJ, Gibbons P. Empirical Support for the Gender-as-Culture Hypothesis: An Intercultural Analysis of Male/Female Language Differences. Hum Commun Res. 2001;27(1):121–52.

35. Bogaers IRWM. Gender in Job Interviews: some implications of verbal interactions of women and men. Int'l. J. Soc. Lang. 1998;129:35-58.

36. Butler J. Gender Trouble. Feminism and the Subversion of Identity. New York: Routledge and Kegan Paul; 1990.

37. Cameron D. Language, gender, and sexuality: Current issues and new directions. APPL LINGUIST. 2005;26(4):482-502.

38. Watson BM, Gallois C. Communication accommodation between patients and health professionals: themes and strategies in satisfying and unsatisfying encounters. International journal of applied linguistics. 1999;9(2):167-80.

39. Bylund CL, Peterson EB, Cameron KA. A practitioner's guide to interpersonal communication theory: An overview and exploration of selected theories. Patient Educ Couns. 2012;87:261–7.

40. Namy LL, Nygaard LC, Sauerteig D. Gender differences in vocal accommodation: the role

of perception. J Lang Soc Psychol. 2002;21(4):422-32.

41. Green JA. Communication Accommodation Theory: Understanding Language Use in Social Interaction. [PhD thesis]. New Zealand: University of Otago; 2003.

42. Soliz J, Giles H. Relational and Identity Processes in Communication: A Contextual and Meta-Analytical Review of Communication Accommodation Theory. Annals of the International Communication Association. 2014;38(1):107-44.

43. Muir K, Joinson A, Cotterill R, Dewdney N. Characterizing the Linguistic Chameleon: Personal and Social Correlates of Linguistic Style Accommodation. Hum Commun Res. 2016;42:462-84.

44. Thomson R, Murachver T, Green J. Where is the gender in gendered Language? Psychol Sci. 2001;12(2):171-5.

45. Green JA. The writing on the stall: Gender and graffiti. J Lang Soc Psychol. 2003;22:282-96.

46. Hancock AB, Rubin BA. Influence of communication partner's gender on language. J Lang Soc Psychol. 2015;34(1):46-64.

47. Turabian JL, Minier-Rodriguez LE, Moreno-Ruiz S, Rodriguez-Almonte FE, Cucho-Jove R, Villarin-Castro A. Gender Differences in Verbal Behavior Style in Interviews in Family Medicine: Mars and Venus, or North Dakota and South Dakota? J Women's Health Care. 2017;6(2).

48. Griffin E. A first look at communication theory. 8th ed. New York: McGraw-Hill; 2012.

49. Wallentin M. Putative sex differences in verbal abilities and language cortex: A critical review. Brain Lang. 2009;108:175-83.

50. Griffin E, Ledbetter A, Sparks G. A first look at communication theory. 9th ed. New York: McGraw-Hill; 2014.

51. Holmes J. Women, Men and Politeness London: Longman; 1995.

52. Leaper C, Ayres MM. A meta-analytic review of gender variations in adults' language use: talkativeness, affiliative speech, and assertive speech. Pers Soc Psychol Rev. 2007;11(4): 328-63.

53. Mulac A, Studley LB, Blau S. The Gender-Linked Language Effect in Primary and Secondary Students' Impromptu Essays. Sex Roles. 1990;23(9):439-69.

54. Mulac A, Giles H, Bradac JJ, Palomares NA. The gender-linked language effect: an empirical test of a general process model. Lang Sci. 2013;38:22–31.

55. Weinberg FJ, Treviño LJ, Cleveland AO. Gendered Communication and Career Outcomes: A Construct Validation and Prediction of Hierarchical Advancement and Non-Hierarchical Rewards. Communic Res. 2015.

56. Mohindra V, Azhar S. Gender Communication: A Comparative Analysis of Communicational Approaches of Men and Women at Workplaces. IOSR-JHSS. 2012;2(1): 18-27.

57. Eunson B. C21 Communicating in the 21st century. 2nd ed. Australia: John Wiley & Sons; 2008.

58. Eagly AH, Carli LL. Women and the labyrinth of leadership. Harvard Business Review. 2007;85:63-71.

59. Hirschman L. Female-male differences in conversational interaction. LANG SOC. 1994;23:427-42.

60. Coates J. Women, men and language: a sociolinguistis account of gender differences in language. 3rd ed. London/New York: Routledge; 2013.

61. Ezard J. Mobile users 'ape monkeys'. The Guardian. 2001 December 5.

62. Moss C. Welcome back football, the great gossip mag for men. Prowess, professionalism, technique, talent? Forget it. Professional football has become the male equivalent of Hello! magazine. The Telegraph. 2015 August 13.

63. Johnson S, Finlay F. Do men gossip? An analysis of football talk on television. In: Johnson S, Meinhof U, editors. Language and Masculinity. Oxford: Blackwell; 1997. 130–43 p.

64. Benwell B. Male goosip and language play in the letters pages of men's lifestyle magazines. J Pop Cult. 2001;34(4):19-33.

65. Bischoping K. Gender differences in conversation topics, 1922-1990. Sex Roles. 1993;28(1):1-18.

66. Michaud SL, Warner RM. Gender differences in self-reported response to trouble talk. Sex Roles. 1997;37(Issue 7–8):527–40.

67. Crawford M. Talking difference: on gender and language. London(UK) & Thousand Oaks (CA): Sage; 1995.

68. McQuiston DH, Morris KA. Gender Differences in Communication: Implications for Salespeople. Journal of Selling & Major Account Management. 2009;9(1):54-64.

69. Holmes J. An Introduction to Sociolinguistics. 3rd ed. Harlow (England)/New York (USA): Pearson Longman; 2008.

70. Hall JA, Friedman GB. Status, gender, and nonverbal behavior: a study of structured interactions between employees of a company. PERS SOC PSYCHOL B. 1999;25(9):1082-91.

71. Hall JA, Roter DL. Do patients talk differently to male and female physicians? A meta-analytic review. Patient Educ Couns. 2002;48(3):217-24.

72. Koppel M, Argamon S, Shimoni AR. Automatically Categorizing Written Texts by Author Gender. Literary and linguistic computing. 2002;17(4):401-12.

73. Ishikawa Y. Gender Differences in Vocabulary Use in Essay Writing by University Students. Procedia Soc Behav Sci. 2015;192:593-600.

74. Argamon S, Koppel M, Fine J, Shimoni A. Gender, genre, and writing style in formal written texts. Text. 2003;23(3):321-46.

75. Newman ML, Groom CJ, Handelman LD, Pennebaker JW. Gender differences in language use: An analysis of 14,000 text samples. Discourse Processes. 2008;45:211-36.

76. Hyde JS. Sex and cognition: gender and cognitive functions. Curr Opin Neurobiol. 2016;38:53–6.

77. OECD. PISA 2015 Results in Focus; 2016.

78. OECD. PISA in Focus Nº 49: What lies behind gender inequality in education? 2015.

79. Merisuo-Storm T. Girls and boys like to read and write different texts. SCAND J EDUC RES. 2006;50(2):111–25.

80. Meece JL, Glienke BB, Burg S. Gender and motivation. Journal of School Psychology. 2006;44:351-73.

81. Lasarte G. Feminización del hábito lector [feminizing the habit of reading]. Ocnos. 2013;9:53-68.

82. Lowrie T, Diezmann CM. Solving graphics tasks: Gender differences in middle-school students. LEARN INSTR. 2011;21:109-25.

83. OECD Skills Studies. The Survey of Adult Skills: Reader's Companion. 2nd ed. Paris: OECD Publishing; 2016.

84. OECD Skills Studies. Skills Matter: Further Results from the Survey of Adult Skills Paris: OECD Publishing; 2016.

85. OECD. Skilled for life? Key Findings from the Survey of Adult Skills; 2013.

86. Tam NT, Huy NT, Thoa LTB, Long NP, Trang NTH, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93(3):186-98.

87. Bergenmar M, Johansson H, Wilking N. Levels of knowledge and perceived understanding among participants in cancer clinical trials – factors related to the informed consent procedure. Clin Trials. 2011;8:77–84.

88. Paris A, Deygas , Cornu , Thalamas C, Maison P, Duale , et al. Improved informed consent documents for biomedical research do not increase patients' understanding but reduce enrolment: a study in real settings. Br J Clin Pharmacol. 2015;80(5):1010-20.

89. Paris A, Nogueira da Gama Chaves D, Cornu C, Maison P, Salvat-Mélis M, Ribuot C, et al. Improvement of the comprehension of written information given to healthy volunteers in biomedical research: a single-blind randomized controlled study. Fundam Clin Pharmacol. 2007;21(2):207-14.

90. Raich PC, Plomer KD, Coyne CA. Literacy, comprehension, and informed consent in clinical research. Cancer Invest. 2001;19(4):437-45.

91. Morrow G, Gootnick J, Schmale A. A simple technique for increasing cancer patients' knowledge of informed consent to treatment. Cancer. 1978;42:793–9.

92. Knepp MM. Personality, sex of participant, and face-to-face interaction affect reading of informed consent forms. Psychol Rep. 2014;114(1):297-313.

93. Lobato L, Bethony JM, Pereira FB, Grahek SL, Diemert D, Gazzinelli MF. Impact of gender on the decision to participate in a clinical trial: a cross-sectional study. BMC Public Health. 2014;14(1156).

94. Carpenter DM, DeVellis RF, Hogan SL, Fisher EB, DeVellis BM, Jordan JM. Use and Perceived Credibility of Medication Information Sources for Patients with a Rare Illness: Differences by Gender. J Health Commun. 2011;16(6):629-42.

95. Chai C, Wu X, Shen D, Li D, Zhang K. Gender differences in the effect of communication

on college student's online decisions. Comput Human Behav. 2016; 65.

96. Zhang KZK, Cheung CMK, Lee MKO. Examining the moderating effect of inconsistent reviews and its gender differences on consumer's online shopping decision. International Journal of Information Management. 2014; 34.

97. Zhang Y, Dang Y, Chen H. Research note: Examining gender emotional differences in Web forum communication. Decision Support Systems. 2013;55(3):851-60.

98. Tsai MJ, Liang JC, Hou HT, Tsai CC. Males are not as active as females in online discussion: Gender differences in face-to-face and online discussion strategies. Australasian Journal of Educational Technology. 2015; 31(3).

99. Fox AB, Bukatko D, Hallahan M, Crawford M. The medium makes a difference: Gender similarities and differences in instant messaging. J Lang Soc Psychol. 2007;26(4):389-97.

100. Guiller J, Durndell A. Student's linguistic behaviour in online discussion groups: Does gender matter? Comput Human Behav. 2007;23(5).

101. Ang CS. Internet habit strength and online communication: Exploring gender differences. Comput Human Behav. 2017;66.

102. Hasan B. Exploring gender differences in online shopping attitude. Comput Human Behav. 2010;26(4).

103. Garbarino E, Strahilevitz M. Gender Differences in the perceived risk of buying online and the effects of receiving a site recommendation. Journal of Business Research. 2004;57.

104. Lian JW, Yen DC. Online shopping drivers and barriers for older adults: Age and gender differences. Comput Human Behav. 2014;37.

105. Muscanell NL, Guadagno RE. Make new friends or keep the old: Gender and personality differences in social networking use. Comput Human Behav. 2012;28(1):107-12.

106. Joiner R, Stewart C, Beaney C, Moon A, Maras P, Guiller J, et al. Publically different, privately the same: Gender differences and similarities in response to Facebook status updates. Comput Human Behav. 2014;39:165-9.

107. Oberst U, Renau V, Chamarro A, Carbonell X. Gender stereotypes in Facebook profiles: Are women more female online? Comput Human Behav. 2016;60:559-64.

108. Kimbrough AM, Guadagno RE, Muscanell NL, Dill J. Gender differences in mediated communication: Women connect more than do men. Comput Human Behav.

2013;29(3):896-900.

109. Wang J, Madnick S, Li X, Alstott J, Velu C. Effect of Media Usage Selection on Social Mobilization Speed: Facebook vs E-Mail. PLoS One. 2015;10(9):e0134811.

110. Young R, Len-Ríos M, Young H. Romantic motivations for social media use, social comparison, and online aggression among adolescents. Comput Human Behav. 2017;75: 385-95.

111. Zheng W, Yuan CH, Chang WH, Wu YCJ. Profile pictures on social media: Gender and regional differences. Comput Human Behav. 2016;63:891-8.

112. Tifferet S, Vilnai-Yavetz I. Gender differences in Facebook self-presentation: An international randomized study. Comput Human Behav. 2014;35:388-99.

113. Scott CF, Bay-Cheng LY, Prince MA, Nochajski TH, Collins RL. Time spent online: Latent profile analyses of emerging adults' social media use. Comput Human Behav. 2017;75(311-9).

114. Gender and Instagram Hashtags: A Study of #Malaysianfood. In: Zhang Y, Baghirov F, Hashim H, Murphy J, editors. Conference on Information and Communication Technologies in Tourism RESEARCH NOTES; 2016.

115. Forgays DK, Hyman I, Schreiber J. Texting everywhere for everything: Gender and age differences in cell phone etiquette and use. Comput Human Behav. 2014;31:314-21.

116. Chen C, Zhang KZK, Gong X, Zhao SJ, Lee MKO, Liang L. Examining the effects of motives and gender differences on smartphone addiction. Comput Human Behav. 2017;75:891-902.

117. Yang F-Y, Huang R-T, Tsai I-J. The effects of epistemic beliefs in science and gender difference on university students'science-text reading: an eye-tracking study. International Journal of Science & Mathematics Education. 2016;14(3).

118. Huang P-S, Chen H-C. Gender Differences in Eye Movements in Solving Text-and-Diagram Science Problems. International Journal of Science and Mathematics Education. 2015;14(S2):327-46.

119. Lorigo L, Haridasan M, Brynjarsdóttir H, Xia L, Joachims T, Gay G, et al. Eye tracking and online search: Lessons learned and challenges ahead. Journal of the Association for Information Science and Technology. 2008;59(7):1041-52.

120. Pan B, Hembrooke HA, Gay GK, Granka LA, Feusner MK, Newman JK, editors. The determinants of web page viewing behavior: an eye-tracking study. Proceedings of the

2004 symposium on Eye tracking research & applications. ACM; 2004.

121. Alt64, AIMC. Estudio Eyetrack Medios España: Análisis del comportamiento visual de los internautas y la efectividad de la publicidad online. España; 2005.

122. Schiessl M, Duda S, Thölke A, Fischer R. Eye tracking and its application in usability and media research. MMI-interaktiv Journal. 2003;6:41-50.

123. Mueller SC, Jackson CP, Skelton RW. Sex differences in a virtual water maze: An eye tracking and pupillometry study. Behav Brain Res. 2008;193(2):209-15.

124. Ha JF, Longnecker N. Doctor-Patient Communication: A Review. The Ochsner Journal. 2010;10(1):38-43.

125. Huang CC, Huang CC, Yang YY, Lin SJ, Chen JW. The influence of gender on the communication skills assessment of medical students. Eur J Intern Med. 2015;26(9):670-4.

126. Ahmed R, Bates BR. To accommodate, or not to accommodate: Exploring patient satisfaction with doctors' accommodative behaviour during the clinical encounter. J Commun Healthc. 2016;9(1):22-32.

127. Bento SF, Hardy E, Osis MJ. Process for obtaining informed consent: women's opinions. Dev World Bioeth. 2008;8(3):197-206.

128. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Medical Ethics. 2013;14:28.

129. Hayman RM, Taylor BJ, Peart NS, Galland BC, Sayers RM. Participation in research: Informed consent, motivation and influence. J Paediatr Child Health. 2001;37:51-4.

130. Stevens PE, Pletsch PK. Informed consent and the history of inclusion of women in clinical research. Health Care Women Int. 2002;23(8):809-19.

131. Street Jr RL. Gender differences in health care provider-patient communication: are they due to style, stereotypes, or accommodation? Patient Educ Couns. 2002;48(3):201-6.

132. Bertakis KD, Helms LJ, Callahan EJ, Azari R, Robbins JA. The influence of gender on physician practice style. Med Care. 1995;33(4):407-16.

133. Roter DL, Hall JA, Aoki Y. Physician gender effects in medical communication: a meta-analytic review. JAMA. 2002;288(6):756-64.

134. Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. Annu Rev Public Health. 2004;25:497-519.

135. Watson B, Gallois C. Nurturing communication by health professionals toward patients: a communication accommodation theory approach. Health Commun. 1998;10(4):343–55.

136. ClinicalTrials.gov. A service of the U.S. National Institutes of Health. [Online]. [cited 2017 07 20. Available from: https://clinicaltrials.gov/ct2/about-studies/glossary.

137. CDC: Center for Disease Control and Prevention. [Online]. [cited 2017 August 29. Available from: https://www.cdc.gov/vaccines/terms/glossary.html.

138. Applied Clinical Trials: The CDISC Glossary of Clinical Research Terminology. [Online].; December 2016/ January 2017. Available from: appliedclinicaltrialsonline.com.

139. "Glossary" Online Ethics Center for Engineering and Science 1/31/2006. [Online]. [cited 2017 August Wednesday 23. Available from: www.onlineethics.org/glossary.aspx.

140. Horizon 2020- The EU framework Programme for Research and Innovation. [Online]. Available from: http://ec.europa.eu/programmes/horizon2020/.

141. Shivayogi P. Vulnerable populations and methods for their safeguard. Perspectives in Clinical Research. 2013 Jan-Mar;4(1).

142. Sheikh A, Halani L, Bhopal R, Netuveli G, Partridge RM, Car J, et al. Facilitating the Recruitment of Minority Ethnic People into Research: Qualitative Case Study of South Asians and Asthma. PLOS Medicine. 2009 October; 6(10).

143. Newington L, Metcalfe A. Factor influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC Medical Research Methodology. 2014;14(10).

144. McGartland Rubio D, Schoenbaum EE, Lee LS, Schteingart DE, Marantz PR, Anderson KE, et al. Defining Translational Research: Implications for Training. HHS Author Manuscripts. 2010 March;85(3).

145. López de Argumedo M, Reviriego E, Andrío E, Rico R, Sobradillo N, Hurtado de Saracho I. Revisión externa y validación de instrumentos metodológicos para la Lectura Crítica y la síntesis de la evidencia científica. Madrid: Plan Nacional para el SNS del MSC. Servicio de Evaluación de Tecnologías Sanitarias del País Vasco (Osteba). Informes de Evaluación de Tecnologías Sanitarias: OSTEBA Nº 2006/02;2006.

146. Durant RW, Wenzel JA, Scarinci IC, Paterniti DA, Fouad MN, Hurd TC, et al. Perspectives on Barriers and Facilitators to Minority Recruitment for Clinical Trials among cancer

Center Leaders, Investigators, Research Staff and Referring Clinicians: Enhancing minority participation in clinical trials (EMPaCT). Cancer. 2014;120(07).

147. The Tech Terms Computer Dictionary. [Online]. [cited 2017 August Wednesday 23. Available from: https://techterms.com/.

148. The Law Dictionary. [Online]. [cited 2017 August 29. Available from: http://thelawdictionary.org.

AGE ISSUES ASSOCIATED WITH THE ACQUISITION OF INFORMED CONSENT: THE MINORS CASE.

B.1. BACKGROUND/PURPOSE

The autonomy of the patient in the decision of participating in clinical research is of major importance, being the informed consent the document that allows the subject voluntarily decide to participate or not. But, what happens when the research involves minors?

Due to its consideration as a vulnerable population and its legal situation, the inclusion of minors in research is a great challenge and should be done with special care, being very important to identify their characteristics and needs. To know what to include in the assent, how to determine the degree of understanding and their competence to decide about the participation in the research are some of the questions that a researcher has to solve.

Regarding the last question, several studies highlighted MacArthur competence assessment tool for clinical research (MacCAT-CR) as a useful tool for assessing the minor's competence.

The aim of this systematic review is to evaluate the contents of the assent and informed consent by minors and whether the MasCAT-CR is a useful tool to evaluate the competence of the minor.

B.2. OBJECTIVES/ REVIEW QUESTION

B.2.1 MAIN OBJECTIVE

- Evaluate the assent and informed consent by minors.

B.2.2 SPECIFIC OBJECTIVES

- Describe the information that should include an informed consent by minors or assent in research.
- Analyse the minor's understanding of each content of the informed consent or assent.
- Evaluate whether MacCAT-CR is a good tool for assessing the competence of a minor to consent in research

B.3. MATERIALS AND METHODS

In order to respond to the objectives set in this task, and to evaluate the state of the art in the three specific objectives identified, a systematic review was carried out as an objective and rigorous methodology to accumulate evidence.

The implementation of a systematic review necessarily involves a series of phases described in the sections developed below and summarized in the flowchart of ***annex B.6.1***.

B.3.1 FORMULATION OF THE PICO QUESTION

The review of the scientific literature in search of evidence requires a correct definition of the research question and the creation of a logical structure to improve the scope of the research.
The PICO strategy, whose acronyms correspond to the terms that should be included in this question, respond to: Population-Intervention-Comparison-Outcome.

The working group agreed on the following research questions that could answer the objectives of the proposed task:

- *What information is relevant to include in the assent / consent of children who want to participate in a research study?*
- *What do minors who decide to participate in a research study understand?*
- *How can we evaluate the competence of a minor to make the decision to participate in a research study?*

B.3.2 SEARCH OF RESEARCH STUDIES

A search strategy was designed in the PubMed database with the following keywords [MeSH/Keywords]:

- Population:
  - Child
  - Minors
  - Adolescent
- Intervention:
  - Informed Consent
    - Informed Consent by Minors
    - Consent Forms
  - Assent [All Fields]
  - Research
  - MacCAT-CR
- Outputs:
  - Decision Making

- Ethics
  - Ethics, Research
  - Ethical Theory
  - Principle-Based Ethics
  - Ethical Analysis
- Comprehension
  - Understanding

Different searches were done combining the keywords and taking into account a list of essential articles contributed by the members of the research team. After checking that the articles considered essential, appeared within the search, it was finally decided to work with the updated formula; making the search on July 10, 2017.

> *((("Informed consent"[Mesh] OR "assent"[All Fields]) AND "Ethics"[Mesh] AND ("Research"[Mesh] OR "Comprehension"[Mesh] OR "MacCAT"[TW])) OR (("Informed Consent By Minors"[TW] OR "Consent Forms"[TW] OR "assent"[All Fields]) AND ("Ethical Theory"[TW] OR "Principle-Based Ethics"[TW] OR "Ethics, Research"[TW] OR "Ethical Analysis"[TW] OR "Comprehension"[TW] OR "Understanding"[TW] OR "Readibility"[TW] OR "MacCAT"[TW] OR "Research"[TW] OR "Clinical research"[All Fields])) OR (("Ethics"[MeSH] OR "Comprehension"[MeSH] OR "MacCAT"[TW]) AND ("Informed consent"[Mesh] OR "assent"[All Fields]) AND "clinical research"[All Fields])) AND ((English[lang] OR Spanish[lang]) AND ("infant"[TW] OR "child"[TW] OR "adolescent"[TW] OR "minors"[TW])) AND ("2007/07/14"[PDat] : "2017/07/10"[PDat])*

After doing the general search it was necessary to review all the abstracts of the studies found to know if they really answered the research question. To that end, inclusion and exclusion criteria had been previously defined, which are reflected below.

B.3.2.1 CRITERIA FOR INCLUDING STUDIES IN THE REVIEW

- Type(s) of study design:
  - Experimental studies/ clinical research
  - Observational studies/ clinical research
  - Theoretical studies/ clinical research
- Type(s) of study participants / sub-populations:
  - Minors.
- Type(s) of interventions:
  - Informed consent by minors or Assent in clinical research.
- Type(s) of outcome measures
  - Contents of the Informed consent/Assent by minors.
  - Comprehension/Understanding of the information included in the Informed consent/Assent.
  - Benefits and harms of using MacCAT-CR
- Type(s) of publications

- Full text
- Abstracts

- Publication date (time period):
  - From 2007/07/14 to 2017/07/10 (last 10 years)
- Language(s):
  - English
  - Spanish

B.3.2.2 CRITERIA FOR EXCLUDING STUDIES FROM THE REVIEW

- Wrong type of study
  - Medical treatment and clinical practise won't be included because I-Consent is focussed on the Informed consent in clinical research.
- Wrong population
  - Researchers
  - Adults, parents, legal guardians
- Wrong purpose
  - When the objective of the study does not refer to the information that is of interest in the assent, or the level of understanding of the child or the assessment of their ability.
- Case Report
  - Singular cases won't be considered in this review.

B.3.3 SELECTING ITEMS

B.3.3.1 PRESELECTION PHASE

In the pre-selection phase, a blind peer review was carried out by reading the titles and abstracts of the articles resulting from the search, and taking into account the inclusion and exclusion criteria.

For that, the list of the studies founded were uploaded to the software Rayyan[(1)] to do the screening. Rayyan is a free web-tool designed to help researchers working on systematic reviews and other knowledge synthesis projects, and dramatically speeds up the process of screening and selecting studies.

Allows blind the review, access to the content of the article (title and abstract) from the same tool, detect duplicates and mark the reason for inclusion and exclusion as the reading is performed.

Pairs of reviewers screened and decided which studies meet the inclusion criteria. Disagreements were resolved through discussion in a group of three people in a verification phase.

The reasons for excluding articles have been recorded.

B.3.3.2 SELECTION PHASE

Reviewers extracted and analysed data independently and in duplicate from each eligible study. When the study design allowed it, the evaluation was done using standardized forms (OSTEBA FLC tools) and the online program (FLC 2.0)[(2)]. FLC 2.0 is a web application designed to support the development of systematic reviews of the scientific evidence providing tools for quality assessment of scientific studies and evidence synthesis.

Osteba (Basque Oficce Health Technology Assessment) has developed methodological instruments called FLC Tools to facilitate this process of Critical Appraisal and to synthesise the scientific evidence for researchers involved in a systematic review.

The critical appraisal process involves not only an assessment of the most important methodological aspects, but it also requires a detailed analysis of the aspects that contribute to the validity of a study. Reviewers resolved disagreements by discussion.

B.3.4 DATA COLLECTION AND CRITICAL READING.

Once the articles that were part of the review were selected, it was necessary to evaluate the internal quality of the studies using the Critical Appraisal Tools.

The data collection sheet ***(Annex B.6.2)*** consists of several sections that ask about the characteristics of the study. By including different types of study, a critical reading sheet was elaborated with different sections depending on whether it was a narrative review or was an empirical study, based on the proposals by the tool FLC 2.0.

The critical reading sheet leads the reviewer to enter the details of the study, collecting the data that produce the tables of evidence ***(Annex B.6.3).***

A critical reading sheet was completed for each of the articles that had passed the 2nd selection phase. At this stage the same reviewers worked as in the selection stage of articles.

B.3.5 CRITICAL EVALUATION OF THE QUALITY OF STUDIES.

Based on the data obtained in the critical reading sheets, and following the quality pattern suggested by OSTEBA, a quality result has been applied, for the content being analyzed as well as for the methodology applied. The results obtained from the method described in each article along with the other criteria (research question, results, conclusions, conflict of interest), allowed to apply the "high", "average" or "low" quality assessment, as can be observe in the following table (table B.1).

Table B.1: Classification of Evidence (OSTEBA) by method and content.

	Method GOOD	Method FAIR	Method POOR
Rest of criteria GOOD	HIGH Quality	MODERATE Quality	LOW Quality
Rest of criteria FAIR	MODERATE Quality	MODERATE Quality	LOW Quality
Rest of criteria POOR	LOW Quality	LOW Quality	LOW Quality
Not classifiable: the study does not provide sufficient information to determine its quality			

When the study under analysis does not provide sufficient information to determine its quality, it has been considered "Not classifiable".

B.4. RESULTS

B.4.1 SEARCH OF RESEARCH STUDIES

In the last updated search on July 10, 2017 a total of 521 articles were obtained in PUBMED, which became 518 after solving the 3 duplicate articles. Seven articles from other databases were included as relevant to the research.

B.4.2 SELECTION OF STUDIES

As a result of the first blind selection phase, 412 of the 518 references were excluded. The main reason for exclusion was the population under study, because although the type of study was adequate and minors were participating, the analysis of the information was extracted from the parents or the researchers about the child's assent. In the same way, many of the studies were discarded by the type of study, because they referred to the assent in clinical practice.

Of the remaining 106 articles, in 16 occurred discrepancies and after being analyzed in groups, it was decided to reject them for not focusing on any of the three key points of consent: information, understanding and competence.

With the 90 articles included in this first screening, it was decided to carry out a second screening phase with the same reviewers and blind, after reviewing the criteria for inclusion and exclusion of articles. The result was the inclusion of 39 articles for in-depth analysis and full-text reading, and the remaining 51 were excluded.

The difficulty in selecting articles was due to the complexity of isolating the subjects under study from others directly related to research assent, such as the factors that influence the decision-making process of the child when he becomes a subject of research: mood, emotions, pressure, state of health, coercion, will, etc.

B.4.3 DATA COLLECTION AND CRITICAL READING

With the 39 articles that were finally selected to be included in this summary of the evidence, and the 7 extracted from other databases that contain relevant information, the data collection and critical reading sheets were completed, the result of which is presented in the tables of evidence (***Annex B.6.3***). The articles were grouped according to the content that could help to respond to each of the objectives.

After the critical reading, 4 of the 46 articles were found to refer to other aspects of the informed consent process, related to decision making, modified consent forms, and stages of moral development of the child.

It was observed that the 46 selected articles had a very different OSTEBA quality, as shown in the following summary table.

Table B.2: Summary of the quality of the evidence and content of the selected articles

	OSTEBA High quality	OSTEBA Moderate quality	OSTEBA Low quality	Not classifiable
INFORMATION	Tait, 2017-b	Dove, 2013 Tait, 2017-a	Twycross, 2008 Roth-Cline, 2013 Baker, 2013	Giesbertz, 2016
UNDERSTANDING	Unguru, 2010 O´Lonergan, 2011 Lee, 2013 Friedman, 2016 Vitiello, 2007*	Scherer, 2007 Miller, 2013 Miller, 2014 Poston, 2016 Blake, 2015 Coors, 2016 Murphy, 2007* Lally, 2014* Grootens, 2015*	Unguru, 2009 Blake, 2011 Chappuy, 2008 Fisher, 2016 John, 2008 Ott, 2013*	Massimo, 2009 *(draft)*
COMPETENCE	Hein, 2014	Raymundo, 2008 Monaghan, 2009 Larcher, 2010 Scherer, 2013 Hein, 2015-a Koelch, 2009 Koelch, 2010 Nelson, 2016*	Leibson, 2015 Alexander, 2015*	Hein, 2012 *(draft)* Hein, 2015-b *(comments previous work)* Hunter, 2007 *(personal comments about Gillick competence)*
OTHER THEMES		Swartling, 2011 *(decision making)*		Espejo, 2011 *(moral development)* Antal, 2017 *(modified forms)* Kumpunen, 2012 *(information method)*

**Addicional records from other data bases*

B.4.4 INFORMATION

Informed assent is a process that respects and promotes autonomy in the child's development, to show his/her opinion and decide on the health or illness processes that affect him/her. In this way the empowerment and development of their moral capacity for the autonomous exercise of future decisions is pursued [3, 4].

Although much has been written about assent in the last twenty-five years, there remain controversial aspects regarding this term, such as the quantity and quality of information to be provided to the child and what they really want and need to know, among others[5, 6].

All potential research subjects should be informed of the relevant aspects of the research, before being included in a research study, to protect their autonomy and voluntariness. Even non-competent people have the right to be informed.

In the case of minors, potential research subjects, it is necessary to select the quantity and quality of this information in the assent process.

B.4.4.1 METHODOLOGICAL ASPECTS

In the review carried out, only 7 articles analyze the information that is provided or should be given to the child during the IC process or assent. Of these, only 1 is of high quality, 2 of moderate quality, 3 of low quality and 1 not classifiable because of the lack of data after the critical reading as seen in Table B.3.

Except for an experimental study, the rest of studies are theoretical or observational. In the two studies involving minors and parents, an interview was used as method of data collection along with a semi-structured questionnaire with open questions.

Table B.3: Studies on the information of the assent, according to the quality of the evidence.

Author, year	Quality	Type of study	Nº subjects
Tait, 2017-b	High	Experimental studies/ clinical research	55 minors/55 parents
Dove, 2013	Medium	Observational studies/ clinical research	443 IC documents
Tait, 2017 -a	Medium	Observational studies/ clinical research	20 experts
Twycross, 2008	Low	Theoretical studies/ clinical research	Not applicable
Roth-Cline, 2013	Low	Theoretical studies/ clinical research	Not applicable
Baker, 2013	Low	Observational studies/ clinical research	20 minors/57 parents
Giesbertz, 2016	Not classificable	Theoretical studies/ clinical research	Not applicable

B.4.4.2 RESULTS

Considering the definition proposed by Tait[7] of "assent", we see that the importance of age-appropriate information is reinforce, taking into account the cognitive and emotional aspects of the child, as we observe in the following definition:

> *"Children who lack the legal authority to provide informed consent per state laws should provide their assent to participate in a research study unless they either lack the cognitive ability, their clinical condition precludes their ability to communicate a choice, or the research holds out the prospect of direct benefit that is only available in the context of the research. Assent is an interactive process between a researcher and child participant involving disclosure of cognitively and emotionally appropriate information regarding, at minimum, why the child is being asked to participate, a description of the procedures and how the child might experience them, and an understanding that participation in the study is voluntary. Children should understand that they can decline participation or withdraw from the study at any time. Assent requires that the child explicitly affirms his or her agreement to participate in a manner that reflects their age-appropriate understanding and that is free of undue influence or coercion. In the absence of an explicit agreement, mere failure of the child to object cannot be construed as assent."*

It is important, according to Tait and agreed by a panel of experts using a Delphi technique[7], to inform why he/she has been chosen to participate, the procedures to be submitted and how he/she might experience them, the benefits indirect if there is no expectation of personal benefit and voluntariness and the right to revoke at any time. The experts consider as a requirement for a meaningful assent, the understanding of this basic information and the child's awareness of how it would affect his/her personal situation.

But one thing is what bioethics experts and pediatric researchers decide, and another quite different is the information priority of children. Even their priorities may differ from what their parents or legal guardians think they might be interested in.

This is demonstrated in another study by Tait [8] comparing research priorities among children, adolescents and their parents, where it was concluded that they differ in some aspects. The information priorities were analyzed using questionnaires about the hypothetical participation in a clinical trial. Both children and parents classified all elements of information (nature, purpose, procedure, direct benefits, indirect benefits, risks, voluntariness, right to withdraw) as important, but younger children (<12 years) placed more emphasis on knowing that their personal information will be kept confidential and less on knowing the purpose of the study and the benefits. Aspects that their parents considered to be very important. Adolescents give more importance in knowing what will be done to them, the direct benefits and the nature of the study compared to younger children, without having differences by sex.

For parents, informational priorities were higher if their child was between 13-17 years old and / or was a girl.

Of interest was that while parents seemed to focus more on the importance of real risks, children seemed more interested in the burden of participation, i.e. how much time it could take the participation and whether it would keep them away from their usual activities. Aspects that are not normally contemplated in the information provided to minors.

Previously, Roth-Cline[9] had already sought evidence regarding the information to be contained in the children's assent. He noted that the regulations did not specify the information needed for the child, but the recommendations of the official bodies indicated that it should include information on the procedures to be carried out, the freedom to choose, the communication of the decision and the possibility to withdraw at any time, regardless of whether the parents are provided with more detailed information. The author concluded that the amount of information that a minor should understand should vary with the child's age and maturity without being able to state with scientific evidence the pieces of information to include in the assent.

Regarding the amount of information, Baker[10] in a qualitative study using coded interviews conducted in 2013, attempted to identify how the IC quality of the children with cancer participating in a phase 1 trial could be improved. Of the interviews conducted to 20 children between the ages of 14 and 21, and those made to the parents, it was found that the most frequent suggestions were relative to the information given during the assent process. Information regarding the risks, benefits, purpose of the study, scientific bases that justify their participation, logistical problems in case of participation and all this through an honest communication, without technicalities, in a comfortable and individualized environment depending on the needs of the child and of his family. They also suggested that written information from the IC should be sent in advance, that other means be used (not only written) and that there should be a summary sheet with the key aspects that should be remembered during the course of the trial.

This individualization of assent according to the needs of the child has also been proposed by Giesbertz[11] in a theoretical study in which she attempted to answer the question of how content and the process of assent should be considered to be a personalized assent in the specific case of biobanks. Although the lack of data of that publication makes its quality unclassifiable, it is stated in that article that for the information to be individualized, it must begin with specific aspects and continue giving more information at the request of the child, using not only the means classical writings, but information technologies. That way we will verify that the child wants to know and wants to decide.

In an analysis of the thematic content of pediatric informed consent models performed by Dove in 2013[12], he observed that only 30% use a specific model. Of the 443 IC models analyzed, 56% do not raise the possibility of dissent, 49% do not pose the possibility of a

future IC if they reach the age of majority, only 26% pose the potential risks from a point psychological, social or financial, 33% do not consider the indirect benefits and only 65% name the possibility of withdrawing at any time. All ICs referred to the right of the parents to access the child's information, but did not refer to the child's right to limit it. Confidentiality is specifically protected (coded) in 58% of documents and anonymized in 9%.

Beuchamp y Childress[13] already established that in order for the communication process within the clinical relationship to be truly effective, one of the important elements was adequate exposure of the information. And it is precisely in the decision-making process that the most important thing is to foster an understanding of the information exchanged. Excess or lack of information should be avoided, as should the use of overly technical language, which could interfere with the processing and understanding of the language and lead to decision making without proper understanding.

Twycross[14] attempted to establish a formula so that the information provided to minors involved in research was appropriate. Through meetings with experts conducted during the Research Society's International Nursing Research Conference, a consensus was reached on the format that the information should have:

- The information must have a manageable length, according to the age and development.
- It should not have a larger extension of an A4 double-sided sheet, as the detailed information can overwhelm the child.
- Information leaflets should be designed so that they can be read, but interactive enough to be involved in the process.
- Language should be appropriate to the child's age and development.
- Images and graphics can be used to increase understanding, but should be simple, clear and familiar.
- Do not just increase the font size of a format designed for older children.
- Information sheets should be printed on paper with the letterhead of the hospital or institution where the research is done.
- The brochures must contain the information necessary for the minor's decision.
- Always respect the confidentiality of data.

Many of these recommendations refer to aspects of readability, both linguistic (grammatical and lexical) and typographic (graphic characters), which will allow the child to read and understand it more easily.

B.4.5 UNDERSTANDING

Measurement of understanding of informed consent or assent requires an operational definition of what "understanding of informed consent" means. Using a Delphi method, Buccini[15] proposed in 2009 a definition that takes into account three previous issues:

- What specific information of an IC should the participants know?
- What does "understanding" mean?
- What methods are there to verify understanding?

All this, together with the integration of new information in the subject's previous knowledge. With all this, she considered the understanding of IC as:

"Informed consent comprehension can be said to occur when the following conditions are met:

> • *There is evidence that a potential participant has integrated his/her current knowledge with the consent information;*
>
> • *The evidence occurs at the time the potential participant decides whether or not to take part in the research study;*
>
> • *At a minimum, the integrated consent information includes the consent requirements stipulated by national and international ethics regulations."*

This definition can be useful in putting forward methods or questionnaires to evaluate understanding.

The systematic review shows that these requirements are imperfectly met.

The methodological and content aspects of IC understanding studies in children and adolescents are reviewed below.

B.4.5.1 METHODOLOGICAL ASPECTS

In the review practiced there are 20 empirical articles of verification of the understanding of IC or of assent in minors. 5 of them have high quality, 9 moderate quality, and 6 low quality.

Six of the articles can be considered as clinical trials given the randomization of several IC models, with further study of their different understanding. The rest of the articles deal with open or closed questionnaires, or semi-structured interviews.

Given the wide variety of models it is difficult to draw conclusions. Following the formal aspects, 11 studies are conducted with healthy children or adolescents (for vaccine studies or for hypothetical future studies) and 7 with sick children participating in clinical trials for cancer, HIV and other diseases. Patients participating in cancer trials are Phase I, II or III, as well as post-marketing.

The lapse between the signing of the IC or assent to the investigation and the study of understanding is also very variable: in some cases the signature is immediate to the presentation of the IC, and in others it is up to 2 years later.

In 13 studies, a questionnaire is made with open or closed questions, with large differences in the number of questions, from 1 to 69, and with open or closed response options, responding in a Visual Analogue Scale, dichotomous (yes / no), with several possible answers, or with the Likert method (from "totally agree" to "totally disagree"). Its answer can be done with the help of the investigators. In 11 of the 13 articles the model of the questionnaire is provided. In other cases the interview is the basis of the analysis, usually with a predetermined structure.

Most studies do not report the year of completion of comprehension tests. Only four of the articles include an assessment of the Intelligence Coefficient of the children or adolescents studied, and in another, a test of literacy and numerical capacity as Lally used in her study[16].

Table B.4: Studies on understanding, according to the quality of the evidence.

Author, year	Quality	Type of study	Nº subjects
Friedman 2016	High	Experimental studies/ clinical research	39
Lee 2013	High	Observational studies/ clinical research	123
O'Lonergan 2011	High	Experimental studies/ clinical research	170
Unguru 2010	High	Observational studies/ clinical research	37
Vitiello 2007*	High	Observational studies/ clinical research	295
Blake 2015	Medium	Experimental studies/ clinical research	120
Coors 2016	Medium	Experimental studies/ clinical research	195
Miller 2013	Medium	Observational studies/ clinical research	20
Miller 2014	Medium	Observational studies/ clinical research	61
Murphy 2007*	Medium	Experimental studies/ clinical research	187
Lally 2014*	Medium	Experimental studies/ clinical research	120
Poston 2016	Medium	Observational studies/ clinical research	4
Grootens 2015*	Medium	Observational studies/clinical research	101
Blake 2011	Low	Observational studies/ clinical research	33
Chappuy 2008	Low	Observational studies/ clinical research	29
Fisher 2016	Low	Observational studies/ clinical research	60
John 2008	Low	Observational studies/ clinical research	73
Ott 2013*	Low	Observational studies/ clinical research	33

** Secondary search*

B.4.5.2 RESULTS

The studies of quality HIGH showed the following results:

Friedman[17] in 2016, examines whether the use of two or seven questions during the on-line assent process in healthy gay or bisexual adolescents, for an on-line behavior study improves the understanding of the information in that assent. Two questions during the process,

relating to voluntariness and research risks, were repeated at the end of the assent process. The probability of correct response had an OR ranging from 3 to 10 in the groups that had encountered them during the assent phase, relative to the group that had only read the assent document. Conclusion: Reinforcement through questions interspersed in the process of assent improves their understanding in concrete aspects.

Lee[18] evaluated the understanding of a modified document in text format with supporting images for a Hepatitis B vaccine trial (Experimental studies / clinical research) in the year 2013. The response to a 6-question questionnaire with dichotomous response (yes / no) showed that 56% of 123 young people between 12 and 17 years old answered all questions correctly. The best understood questions were those concerning randomization and the possibility of withdrawal from the study. The worst-understood issue was that of the blinding choice of vaccine.

O'Lonergan[19] in 2011 studied the difference in understanding between a classic CI model in text format or a multimedia one for hypothetical imaging studies. A questionnaire of 8 questions after the IC process showed a better understanding among those who had used the multimedia model ($p < 0.009$), especially in relation to the sections of study procedures and risks. The study was done in parallel with the parents, and both the parents and the children had a better subjective impression of understanding than the questionnaire showed.

If the previous studies were hypothetical models in healthy population, Unguru[4] in 2010 studied children with cancer through a questionnaire of 69 questions and with the help of an interviewer. Analyzes the degree of understanding about the Experimental studies / clinical research in which they are participating, and whose IC was signed more than 4 months earlier. In the understanding aspect, 70% of minors reported that the information provided at that moment was difficult or very difficult to understand, especially for the language used.

In MODERATE quality studies, two studies by Miller[20, 21] and Poston[22] also use cancer patients. In the study published by Miller in 2013[21] she uses a verbally administered structured interview after 6 days of the IC process for a Phase I Experimental studies / clinical research, on a questionnaire that deals with aspects of understanding and decision making. Overall, researchers have a good understanding of volunteerism and risk, although a significant percentage (30%) expected direct benefits. In the article that Miller published in 2014[20] , also with interviews, she found a good understanding, with a value of comprehension difficulty of 1.94 (on a scale between 1, very easy to understand, and 10, very difficult to comprehend), comprehension which is believed to be facilitated by good communication with researchers.

Poston[22] finds a questionnaire with quantitative results, an understanding of 64 out of 100 possible points. The small number of participants (n = 4) prevents further conclusions.

Blake[23] in 2015 develops a clinical trial (Experimental studies / clinical research) to see if the understanding of a multimedia IC is better than a traditional model, for a hypothetical HIV vaccine. There is no difference in compression between both IC models.

Murphy[24] did a similar study in 2007 which compares the understanding of a simplified IC with images versus a standard one for a hypothetical study of HIV vaccine in adolescents conducted at three centers. The questionnaire of 19 questions was passed immediately after the live speech of the IC. Unlike the previous study, adolescents with the standard model correctly answered fewer questions than the simplified model (median 14 and 16 correct answers on 19, p = 0.005). The variables associated with better understanding were the IQ, the type of IC read, and the origin of the adolescent.

From the same group (ATN, Adolescent Trial Network for HIV / AIDS Interventions) is Lally's article[16] that demonstrates a better understanding of specific aspects of IC such as "randomization" and "adverse effects" when completing information from a CI for a hypothetical HIV vaccine trial with a booklet explaining these issues with double messages (presentation of a misconception refuted with factual information).

A comic can also be a vehicle for information to get an acceptable understanding of the basics of research, as shown by Gootens-Wieger [25], in which a comic done by professionals about a hypothetical clinical trial in healthy children from 10 to 14 years old shown a comprehension above 65% in the eight sections considered essential in assent/consent to minors (voluntary, ineffective drug, withdrawal, randomization, placebo, side effects, anonymity, benefit uncertainty).

Finally, and within the MODERATE quality studies, the Coors article[26] studies the understanding of a specific IC model, that of a biobank in a sample of adolescents with substance use disorder. In this case, an improved IC model following a discussion process, and focused on current risks improved general understanding through a 6-question questionnaire.

But risks are not always as important to the adolescent as the aversion they may feel to certain procedures such as venipuncture. This is described by Scherer[27] in a theoretical study on the key issues related to the child's assent to research, which concludes that there are differences in the understanding between adolescents and their parents about the appreciation of risks and procedures.

The six LOW quality studies have some interesting aspects.

Blake[23] proposes to put more emphasis on the concepts of "randomization", "placebo", differentiation between clinical practice and research, after interviewing 33 healthy adolescents.

Chappuy [28] in children with cancer or HIV, and also with guided interviews found worse understanding in aspects of procedures, possibility of alternative treatments, length of participation, right of withdrawal, and voluntariness.

Fisher[29] in sexual minority adolescents, and in the face of a hypothetical HIV vaccine, found an acceptable understanding behind the vision of an informative video on risks, benefits, and adherence, and proposes in a similar situation the possibility of self-consent informed.

In a study of healthy children who had participated in a study of a vaccine, done by John[30] in 2008, it is concluded that most children aged 6-8 do not have the ability to understand the factors surrounding a study research, with marked individual differences. Half of the 73 children who participated didn't know why they had blood drawn. Even after explaining and extracting them, 33% still without knowing the answer. Not so with the possibility of withdrawing from the study, which was understood by the majority from the beginning.

Finally, Ott[31], member of the ATN group, found through interviews analyzed with a method based on grounded theory, improved understanding through the interviews themselves, although with incomplete understanding of aspects related to randomization and the need for placebo.

The review of the secondary literature focused on the systematic review and meta-analysis performed by Thanh Tam [32] in 2015, with a bibliographic search until 2013, for understanding IC in adults and children. The three research articles she found and in which minors participate (Chappuy 2008, Miller 2013, and Unguru 2010) are also referenced in this study.

The article by Massimo[33] is rejected because, although it provides a model for analyzing the understanding of an IC, it is only a research project.

B.4.5.3 CONCLUSIONS

The measurement of the understanding of informed consent in research is done through questionnaires or interviews, none validated, and with a high subjective component. It is therefore urgent to have a validated tool, which can be applied in different types of clinical trials, to measure the understanding of informed consent and assent in children and adolescents, as Lepola states[34].

The studies analyzed show contradictory results regarding the application of improved models (with intermediate questions during the process, with multimedia tools, with improved models thanks to previous surveys ...) to improve the understanding.

Different scenarios (studies of hypothetical future clinical trials in the healthy population, or clinical trials in children and adolescents with serious illnesses) probably require different communicative tools on the part of the professionals involved, but in all of them the

importance of effective communication will be present in the IC process, as well as more readable, simplified, and sufficiently informed IC models to improve their understanding.

B.4.6 ASSESING COMPETENCE

It is analyzed here if the child has the capacity to understand the different aspects that entails their participation in a research study.

Logically this section is closely related and includes the above on understanding. In fact, it is the first section of a formal decision-making process called the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).

The capacity, linked to the complementary term of competence, establishes a point or level in which it would be acceptable for the minor to have a voice in the decision to participate, according to Hein[35].

According to Katz[36] the capacity would be *"a clinical determination that adresses the integrity of mental abilities"* while competition would be the legal determination that deals with the social interest of restricting decision making when capacity is in doubt.

The capacity for autonomy is a continuous variable, but competition is dichotomous (whether or not it is competent), and therefore has a greater legal nuance according to Larcher[37]. This author defines competence as *"the ability to understand nature, purpose and consequences and ability to decide"*.

An approach to the competition could be done with a battery of questions:

- What is the illness/condition and what are its effects?
- What treatments/investigations are necessary and why?
- When does this need to be done?
- What does the treatment mean to me, and how will it affect my life?
- What happens if I do not have the treatment?
- What are the alternatives and their effects?
- What are the practical consequences for me and my family on school and friends?

With this we see that the competition is contextual to the environment and to the situation that is sought to certify. Although the capacity required to agree to participate in a research study because of the risk involved is not the same, to assert itself in clinical practice, Monaghan[38] stated in a descriptive study with children aged 12-14 years that should use the exchange of information, the explanation and understanding of such information and the opportunity to ask questions as a basis for capacity assessment.

B.4.6.1 METHODOLOGICAL ASPECTS AND RESULTS

In the review done only 6 articles with empirical content that analyze a validated tool for the determination of the child's capacity to assent in clinical research have been found. This is the MacCAT-CR test.

Four of the articles are from two groups of authors. Hein has made the largest study using the MacCAT-CR tool, originally designed for adults. The authors redesigned it for use in minors, and added two more questions[39].

The MacCAT-CR test is a semi-structured interview that measures the 4 aspects to be evaluated in the determination of the competence of a subject:

- Understanding information.
- Reasoning in the decision-making process.
- Appreciation of the effects of participation in the subject.
- Expression of an election about that participation.

The test has two parts: 15-20 minute interview and a competition ranking.

The authors describe which factors are child-specific to make a judgment of competence: factors related to aspects of development (abstract thinking, cognitive social aspects, changing circumstances for child development, etc.), provision of information (adapted to age of the child, in small blocks, with multimedia support ...), and systemic influences (of parents, friends, and professionals).

The questions added by Hein et al.[39] were: "What do you think your parents will think about whether or not you take part in the study?" and; "What about your friends?".

Later they proved their validity in a study with 161 patients between 6 and 18 years who were participating in different clinical trials or observational studies. The application of the MacCAT-CR test in these patients sought two objectives: to study their reliability and validity in comparison to a clinical capacity assessment and to establish age limits of capacity or lack thereof [40].

For this, the minors were interviewed, with later analysis of the recording, and the authors established a clinical capacity criterion. This result was compared with clinical assessment. The authors found that the test was reproducible and valid, with a concordance with clinical assessment. Based on their results, they found that under 9.6 years the child was probably not capable, and that over 11.2 years was able, with the intermediate values being a gray zone of probable need for assessment on a case-by-case basis.

The same working group analyzes the factors that determine competition through a multivariate analysis of the previous study. It is not surprising that age and IQ are the variables that most influence capacity [41].

Koelch et al. published two similar studies[42, 43] with two small groups of adolescents with ADHD (with or without oppositional defiant disorder added). In the first study[43] they invited

them to participate in an open study on the understanding of a possible Experimental studies / clinical research, using the MacCAT-CR test. This use seemed more meant to measure understanding, appreciation and reasoning, than to a decision of competence or not: With this premise they found a more deficient understanding in the more abstract subjects (what is the final objective of an Experimental studies / clinical research, and what is the randomization and nature of the placebo).

In the 2010 publication[42], also involving a small sample with the same diseases, the MacCAT-CR test was passed to 12 adolescents and 12 parents to determine their competence to participate in an Experimental studies / clinical research with psychostimulants. From each minor the authors made a clinical assessment of competence, which was positive in all of them. MacCAT test scores for ability were better in parents than in minors. They didn't find correlation between capacity and IQ. The worst-understood items were those referring to the purpose of the study, nature of the placebo and possible absence of benefit for the patient).

Nelson in 2016[44] adapted the MacCAT-CR test to perform it during the informed consent process instead of after it, as usually done, and simplifies the contribution of information given. It also studies variables that may influence capacity. It studies 30 adolescents between 14 and 21 years old. They demonstrate a capacity similar to adults, although the variables studied, age, level of literacy, and socioeconomic level influence the degree of ability.

Alexander in 2015[45] studied 33 adolescents aged 16-19 years on a hypothetical HIV vaccine, through interviews with an ethnographic content analysis, and following the MacCAT-CR scheme with its four points (although without referring to it), found that all are competent to decide whether to participate in that hypothetical study.

Table B.5: Studies on competence, according to the quality of the evidence.

Author, year	Quality	Type of study	Nº subjects
Hein 2014	High	Observational studies/ clinical research	161
Hein 2015	Moderate	Observational studies/ clinical research	161
Koelch 2009	Low	Observational studies/ clinical research	19
Koelch 2010	Moderate	Observational studies/ clinical research	12
Nelson 2016	Moderate	Observational studies/ clinical research	30
Raymundo 2008	Moderate	Observational studies/ clinical research	59
Alexander 2015	Low	Observational studies/ clinical research	33

In addition to the MacCAT-CR, other authors have evaluated the possibility of using other models to assess the ability to consent. Thus, Raymundo[46] evaluated the moral development of a group of minors with an indicator of consent capacity, based on the Loevinger model of the Ego Stages and using the Souza questionnaire validated and adapted by the author. Raymundo concluded that the ability to understand and decide is gradually acquired, and not suddenly when a child reaches legal capacity. In fact, it is usually purchased before this. But

moral capacity is individual and varies with the person. It states that age, by itself, is not an adequate variable to measure the child's ability to decide, in the process of assent.

B.4.6.2 THEORETICAL STUDIES

Faced with the scarcity of empirical data, theoretical studies have been somewhat more frequent.

A first discussion is developed around the "Gillick competition". This concept comes from the Gillick v West Norfolk & Wisbech Area Health Authority and the Department of Health and Social Security[47] which established that, for clinical practice, the child under the age of 16 was considered competent when the physician determines it. That is useful in clinical practice to solve with agility situations in which there is a priori doubts about the competence of the minor to take of decisions, but according to Hunter[48] it would not be applicable to the investigation.

A Delphi study with 20 experts developed by Tait in 2017, studied the recommendation of the different methods to study the capacity [7]. Interestingly the experts leave the MacCAT-CR test in penultimate place. Table B.6 show the most valued items and its ranking.

Table B.6: Evaluate methods for assessing the child's capacity [7].

ÍTEM	EVALUATE
Discussion with both parents and children to find out their cognitive ability	30
Check feedback for understanding	20
Discussion with the child only to find out their cognitive ability	10
Use of general developmental models (eg, child or adolescent)	10
Based on age cut-off points	5
Use a short examination to find understanding	0
Using a standardized tool (b.p. the MacCAT-CR)	0
Only discussion with parents	0

It is still argued whether age should be the sole or main criterion for defining competence for assent. Hein[35] defends the age criterion, but not Schrerer[49]. Leibson's[50] review of IC in pediatric research, show how different authors suggest the age of 9 years as a cut between non-competition and competition, although this assertion is not shared by others.

B.4.6.3 CONCLUSIONS

Analysis of decision-making capacity for assent in children and adolescents remains controversial.

If the MacCAT-CR test, used in adults and modified for children and adolescents has proved valid, experts are still discussing whether to establish age competition, to use the MacCAT-CR test on each occasion or to use methods based on in interaction with the researcher and parents.

B.5. BIBLIOGRAPHY

1. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan- a web and mobile app for systematic reviews. Systematic Reviews. DOI: 10.1186/s13643-016-0384-4; 2016; Available from: https://rayyan.qcri.org/.

2. López de Argumedo M, Reviriego E, Andrío E, Rico R, Sobradillo N, Hurtado de Saracho I. Revisión externa y validación de instrumentos metodológicos para la Lectura Crítica y la síntesis de la evidencia científica. Madrid: Plan Nacional para el SNS del MSC. Servicio de Evaluación de Tecnologías Sanitarias del País Vasco (Osteba)2006.

3. Bustamante BJP, Díaz RG. Asentimiento y consentimiento informado en pediatría: aspectos bioéticos y jurídicos en el contexto colombiano. Revista Colombiana de Bioética Universidad El Bosque. 2013;8(1):144 - 64.

4. Unguru Y, Sill AM, Kamani N. The experiences of children enrolled in pediatric oncology research: implications for assent. Pediatrics. 2010;125(4):e876-83. Epub 2010/03/31.

5. Unguru Y. Making sense of adolescent decision-making: challenge and reality. Adolescent medicine: state of the art reviews. 2011;22(2):195-206, vii-viii. Epub 2011/11/24.

6. Unguru Y, Coppes MJ, Kamani N. Rethinking pediatric assent: from requirement to ideal. Pediatr Clin N Am. 2008;55(1):211-22.

7. Tait AR, Geisser ME. Development of a consensus operational definition of child assent for research. BMC medical ethics. 2017;18(1):41. Epub 2017/06/11.

8. Tait AR, Geisser ME, Ray L, Hutchinson RJ, Voepel-Lewis T. Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want? Academic pediatrics. 2017. Epub 2017/06/14.

9. Roth-Cline M, Nelson RM. Parental permission and child assent in research on children. The Yale journal of biology and medicine. 2013;86(3):291-301. Epub 2013/09/24.

10. Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. Cancer. 2013;119(23):4154-61.

11. Giesbertz NA, Melham K, Kaye J, van Delden JJ, Bredenoord AL. Personalized assent for pediatric biobanks. BMC medical ethics. 2016;17(1):59.

12. Dove ES, Avard D, Black L, Knoppers BM. Emerging issues in paediatric health research consent forms in Canada: working towards best practices. BMC medical ethics. 2013;14:5. Epub 2013/02/01.

13. Beauchamp T, Childress J. Principios de Ética Biomédica: Ed. Oxford University Press; 2001.

14. Twycross A, Gibson F, Coad J. Guidance on seeking agreement to participate in research from young children. Paediatric nursing. 2008;20(6):14-8.

15. Buccini L, Caputi P, Iverson D, Jones C. Toward a construct definition of informed consent comprehension. J Empir Res Hum Res Ethics. 2009;4(1):17-23.

16. Lally M, Goldsworthy R, Sarr M, Kahn J, Brown L, Peralta L, et al. Evaluation of an intervention among adolescents to reduce preventive misconception in HIV vaccine clinical trials. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2014;55(2):254-9. Epub 2014/03/13.

17. Friedman MS, Chiu CJ, Croft C, Guadamuz TE, Stall R, Marshal MP. Ethics of Online Assent: Comparing Strategies to Ensure Informed Assent Among Youth. Journal of empirical research on human research ethics : JERHRE. 2016;11(1):15-20.

18. Lee S, Kapogiannis BG, Flynn PM, Rudy BJ, Bethel J, Ahmad S, et al. Comprehension of a simplified assent form in a vaccine trial for adolescents. Journal of medical ethics. 2013;39(6):410-2. Epub 2013/01/26.

19. O'Lonergan TA, Forster-Harwood JE. Novel approach to parental permission and child assent for research: improving comprehension2011 2011-1-1. 917-24 p.

20. Miller VA, Baker JN, Leek AC, Drotar D, Kodish E. Patient involvement in informed consent for pediatric phase I cancer research. Journal of pediatric hematology/oncology. 2014;36(8):635-40.

21. Miller VA, Baker JN, Leek AC, Hizlan S, Rheingold SR, Yamokoski AD, et al. Adolescent perspectives on phase I cancer research. Pediatric blood & cancer. 2013;60(5):873-8.

22. Poston RD. Assent Described: Exploring Perspectives From the Inside. Journal of pediatric nursing. 2016;31(6):e353-e65.

23. Blake D, Lemay C, Maranda L, Fortenberry J, Kearney MH, Mazor K. Development and evaluation of a web-based assent for adolescents considering an HIV vaccine trial. AIDS care. 2015;27(8):1005-13.

24. Murphy DA, Hoffman D, Seage GR, 3rd, Belzer M, Xu J, Durako SJ, et al. Improving comprehension for HIV vaccine trial information among adolescents at risk of HIV. AIDS care. 2007;19(1):42-51.

25. Grootens-Wiegers P, de Vries MC, van Beusekom MM, van Dijck L, van den Broek JM. Comic strips help children understand medical research: targeting the informed consent procedure to children's needs. Patient education and counseling. 2015;98(4):518-24. Epub 2015/01/24.

26. Coors ME, Raymond KM, Hopfer CJ, Sakai J, McWilliams SK, Young S, et al. Adolescents with substance use disorder and assent/consent: Empirical data on understanding biobank risks in genomic research2016 2016-1-1. 267-71 p.

27. Scherer DG, Annett RD, Brody JL. Ethical issues in adolescent and parent informed consent for pediatric asthma research participation2007 2007-1-1. 489-96 p.

28. Chappuy H, Doz F, Blanche S, Gentet JC, Tréluyer JM. Children's views on their involvement in clinical research. 2008;50(5):1043-6.

29. Fisher CB, Arbeit MR, Dumont MS, Macapagal K, Mustanski B. Self-Consent for HIV Prevention Research Involving Sexual and Gender Minority Youth: Reducing Barriers Through Evidence-Based Ethics. Journal of empirical research on human research ethics : JERHRE. 2016;11(1):3-14.

30. John T, Hope T, Savulescu J, Stein A, Pollard AJ. Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research? Archives of disease in childhood. 2008;93(5):379-83.

31. Ott MA, Alexander AB, Lally M, Steever JB, Zimet GD, Adolescent Medicine Trials Network for HIVAI. Preventive misconception and adolescents' knowledge about HIV vaccine trials. Journal of medical ethics. 2013;39(12):765-71.

32. Tam NT, Huy NT, Thoa le TB, Long NP, Trang NT, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bulletin of the World Health Organization. 2015;93(3):186-98H. Epub 2015/04/18.

33. Massimo LM, Calcagno A, Battaglia T, Pistorio A. A project for the evaluation of awareness of under-aged patients involved in clinical trials. Development of the IGG-Awareness Scale. Minerva pediatrica. 2009;61(5):483-8.

34. Lepola P, Needham A, Mendum J, Sallabank P, Neubauer D, de Wildt S. Informed consent for paediatric clinical trials in Europe. Archives of disease in childhood. 2016;101(11):1017-25.

35. Hein IM, De Vries MC, Troost PW, Meynen G, Van Goudoever JB, Lindauer RJ. Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research. BMC medical ethics. 2015;16(1):76.

36. Katz AL, Webb SA, Committee On B. Informed Consent in Decision-Making in Pediatric Practice. Pediatrics. 2016;138(2).

37. Larcher V, Hutchinson A. How should paediatricians assess Gillick competence? 2010;95(4):307-11.

38. Monaghan N, Morgan MZ. Consent of older children participating in BASCD coordinated dental epidemiology surveys in Wales2009 2009-1-1. 157-61 p.

39. Hein IM, Troost PW, Lindeboom R, de Vries MC, Zwaan CM, Lindauer RJ. Assessing children's competence to consent in research by a standardized tool: a validity study. BMC pediatrics. 2012;12:156.

40. Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, van Goudoever JB, et al. Accuracy of the MacArthur competence assessment tool for clinical research (MacCAT-CR) for measuring children's competence to consent to clinical research. JAMA pediatrics. 2014;168(12):1147-53. Epub 2014/10/16.

41. Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, van Goudoever JB, et al. Key factors in children's competence to consent to clinical research. BMC medical ethics. 2015;16(1):74.

42. Koelch M, Prestel A, Singer H, Schulze U, Fegert JM. Report of an initial pilot study on the feasibility of using the MacArthur competence assessment tool for clinical research in children and adolescents with attention-deficit/hyperactivity disorder. J Child and Adol Psycofarm. 2010;20(1):63-7.

43. Koelch M, Singer H, Prestel A, Burkert J, Schulze U, Fegert JrM. "...because I am something special" or "I think I will be something like a guinea pig": information and assent of legal minors in clinical trials--assessment of understanding, appreciation and reasoning. Child and adolescent psychiatry and mental health. 2009;3(1):2.

44. Nelson LR, Stupiansky NW, Ott MA. The Influence of Age, Health Literacy, and Affluence on Adolescents' Capacity to Consent to Research. J Empir Res Hum Res Ethics. 2016;11(2):115-21.

45. Alexander AB, Ott MA, Lally MA, Sniecinski K, Baker A, Zimet GD, et al. Adolescent decision making about participation in a hypothetical HIV vaccine trial. Vaccine. 2015;33(11):1331-7.

46. Raymundo MM, Goldim JR. Moral-psychological development related to the capacity of adolescents and elderly patients to consent2008 2008-1-1. 602-5 p.

47. Great Britain. England. Court of Appeal CD. Gillick v West Norfolk and Wisbech Area Health Authority. The all England law reports. 1984;1985(1):533-59.

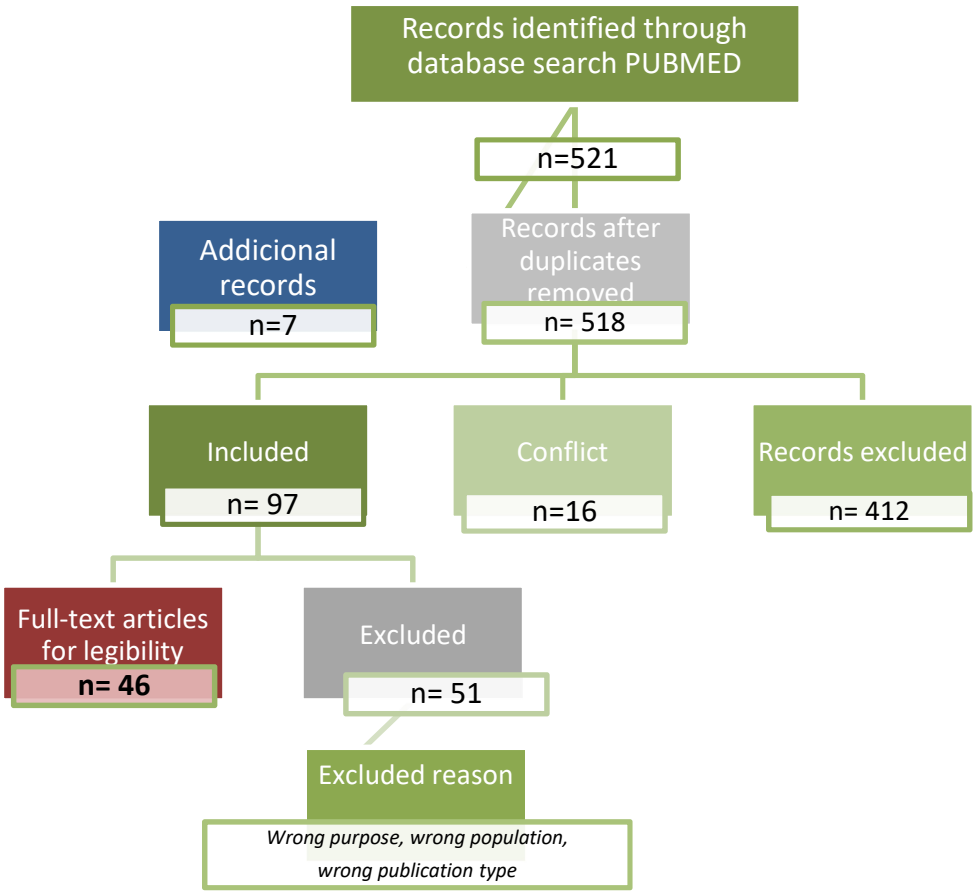
48. Hunter D, Pierscionek BK. Children, Gillick competency and consent for involvement in research. Journal of medical ethics. 2007;33(11):659-62.

49. Scherer DG, Brody JL, Annett RD, Turner C, Dalen J, Yoon Y. Empirically-derived Knowledge on Adolescent Assent to Pediatric Biomedical Research. AJOB Prim Res. 2013;4(3):15-26.

50. Leibson T, Koren G. Informed consent in pediatric research. Paediatric drugs. 2015;17(1):5-11.

B.6. ANNEXES

B.6.1 FLOW DIAGRAM



B.6.2 TEMPLATE FOR THE COLLECTION OF CRITICAL READING DATA

1. REFERENCE
    a. Bibliographic citation in Vancouver style
    b. Brief appointment. It is the one that appears in the summary table
2. STUDY
    a. Study design
    b. Goals
    c. Search period (if systematic review) and / or completion of the study
    d. Origin of the population; type of center and population
    e. Participating entities
3. REVIEWERS; people who perform the critical reading and date in which it is performed.
4. RESEARCH QUESTION
    a. Is the target population adequately defined?

    ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

    b. Is the intervention (s) being studied adequately defined?

    ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

    c. Is the intervention with which to compare or the effects to be studied adequately defined?

    ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

    The study is based on a clearly defined research question

    ☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

5. METHOD
    a. SELECTION CRITERIA
        i. Is the method of selecting the participants / studies included in the review described?

        ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

        ii. Are the inclusion criteria specified?

        ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

        iii. Are the exclusion criteria specified?

        ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

        iv. Were all selected cases / studies included in the study?

        ☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

v. Are the number of studies / participants included?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

vi. In short: are the inclusion and exclusion criteria adequate to be able to answer the question?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

vii. Is the search strategy / characteristics of the participants detailed?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

viii. In summary: is the bibliographic search sufficiently exhaustive and rigorous? Are the participants adequate?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

b. QUALITY OF STUDIES (IF SYSTEMATIC REVIEW)

i. Is the method used to evaluate the quality of studies described?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

ii. In summary: is the quality of the studies evaluated appropriately?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

c. EXTRACTION OF DATA (YES SYSTEMATIC REVIEW)

i. Is any form used for data extraction?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

ii. Is the information about the intervention and results clear for all relevant subjects and groups?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

iii. Are the number of reviewers mentioned?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

iv. In summary: the extraction of data is done rigorously?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

d. INTERVENTION (IF EXPERIMENTAL)

i. Is the study intervention well described?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

ii. Were the same variables measured and the same measurement scales used?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

iii. In summary, the intervention is developed in a rigorous way?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

e. TRACKING (IF EXPERIMENTAL)

i. Is the follow-up period indicated?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

ii. If losses occurred, indicate the number and characteristics of the losses.

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

iii. The method of collecting information is described

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

iv. In short, is follow-up adequate?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

The methodology (empirical study) used guarantees the internal validity of the study

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

The methodology used (narrative review) for the selection and evaluation of individual studies is well described and adequate

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

6. RESULTS

a. Is there a detailed description of the results?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

b. Are the number of studies and patients / participants included in the systematic review evaluated?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

c. Is the quality of the studies included in the review evaluated? In case the quality of the studies is evaluated, write down the results in this regard

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

d. Are the data from the studies included in the review well described?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

Are the results correctly described?

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

7. CONCLUSIONS

a. Do the findings give an answer to the objectives of the study?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

The conclusions are based on the results obtained and take into account the constraints

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

8. CONFLICT OF INTEREST

a. Is the source of funding mentioned?

☐ Yes ☐ No ☐ Partly ☐ N/Not applicable

b. Do the authors declare the existence or absence of any conflict of interest?

The results and conclusions are free from influences derived from conflicts of interest

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

9. EXTERNAL VALIDITY

The results of the review are generalizable to the population and to the context of interest

☐ *Good* ☐ *Fair* ☐ *Poor* ☐ *N/Not applicable*

10. QUALITY OF THE STUDY

Taking into account the answers, the quality of the evidence provided by the study analyzed is assessed.

	METHOD OK	METHOD Medium	METHOD Wrong
Rest of criteria OK	HIGH Quality	MODERATE Quality	LOW Quality
Rest of criteria MEDIUM	MODERATE Quality	MODERATE Quality	LOW Quality
Rest of criteria WRONG	LOW Quality	LOW Quality	LOW Quality

Not classifiable: the study does not provide sufficient information to determine its quality

The quality of evidence is:

☐ High ☐ Medium ☐ Low ☐ Unclassifiable

B.6.3 TABLES OF EVIDENCE.

All critical reading tables completed for the selected articles are listed below.

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Alexander 2015	Design: An observational study with intervention, based on interviews and an analysis of ethnographic content, that focuses on the process (how is the ability of some adolescents to make a decision to enter a hypothetical clinical trial of an HIV vaccine). Goals: Examine the decision-making process of adolescents about their participation in an HIV vaccine trial Period of realization: Not known	Number of participants / group: 33 adolescents aged 16-19 Participating Features: Adolescents of both sexes of 16-19 years, HIV negative and with sexual activity with men, and with desire to participate. Recruitment in clinics, youth agencies and youth programs	Intervention: 4 aspects treated in the interviews (they are the same as those of MacCAT-Cr): - Understanding of relevant information. - Assessment of the situation itself. - Reasoning about options. - Election Follow-up period: Do not Toll: Do not	- Understanding of relevant information: Acceptable. - Assessment of the situation itself: They generally understood that the trial was an experiment, not a prevention measure. They discussed aspects of stigmatization. One more reason to participate acknowledged that it was monetary compensation. - Reasoning about the options: Most would like other people to participate in decision making (in order of frequency, peers, health, family, other adults). - Election: All participants felt able to make a choice.	They show that in the analyzed sample the adolescents have the capacity for an IC. They use the same guide as the MacCAT-CR, without naming it	Not reproducible	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Antal 2017	Design: Observational study for the creation of a multimedia informed consent model in a clinical trial of childhood asthma, and its application. It seeks to increase understanding by reducing the cognitive load Goals: Describe the procedures used in designing and developing a multimedia platform to obtain parental consent and the child's consent for a controlled clinical trial to evaluate a treatment for asthma. Illustrate how five basic principles of multimedia learning were actively incorporated into the multimedia platform Evaluate understanding of parents and adolescents and satisfaction with the use of this platform. Period of realization: The evaluation of the platform, in 2017	Number of participants / group: Not applicable Participating Features: N / Not Applicable	Intervention: Use of a multimedia platform to obtain Informed Consent in asthma research. Comparison, for purposes of understanding, with a classic Informed Consent model. After viewing the video, an understanding questionnaire of 17 items, independently of parents and adolescents, is passed to the 4 days. Follow-up period: N / Not Applicable Toll: N / Not Applicable	In order to elaborate this multimedia, five basic principles of multimedia learning were taken into account: 1) Sensory modality: based on the cognitive learning theory, according to which people have independent channels to process visual and auditory information. 2) Coherence: Redundancy: subjects learn better from images + narration than from images + narration + Narration: better learning if there are signs in the image that show how the content is organized. written text5) Personalization: learning improves with a narrator who acts as a conductor. A video of 15 minutes, with 4 sections, is made interactive (the step to the next section is done after answering a questionnaire of 3 questions). It describes the formal characteristics of the platform and its elaboration (use of professionals of the image and of actors ...).	Studies of published electronic informed consent models do not capture all the components used in this study: Evidence-based learning principles for a CI multimedia format, a complex and real clinical trial, and the inclusion of both parents and minor , in the consent process. Limitations: do not study which of the 5 theoretical items used to make the video may be more important. Costs can be prohibitive. The clinical trials committee must be available for an iterative processing process. Your results (in future publications) will be interesting.	Description of the theoretical bases to develop a multimedia platform for Informed Consent in clinical research with minors. Description of the steps taken to prepare them. Description of the project to analyze your understanding.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Baker 2013	Design: Prospective observational study. It is the secondary analysis of data collected in a larger study in 6 pediatric cancer centers in the USA and that studied the communicative and understanding aspects of informed consent in a phase 1 trial. These data were collected through interviews with parents and adolescents who had already agreed to participate in those phase 1 trials. Goals: To identify the suggestions of parents and adolescents to improve the quality of IC in a phase 1 clinical trial. Period of realization: Not known	Number of participants / group: 57 parents (72% mothers) and 20 children completed the questionnaire Participating Features: Partially Described	Intervention: 85 families were invited to participate in phase 1 studies, and the IC interview was recorded. Subsequently, only those who had agreed to participate in the clinical trial were given a semi-structured interview. One of the questions was: "In your opinion, how can we improve the IC process in a phase 1 study?" The interviews were for parents and children between 14 and 21 years old. The analysis of the answers to the described question was by a qualitative method with analysis of the semantic content. Follow-up period:	There were 220 suggestions (parents) and 54 suggestions (children), which could be grouped into 21 codes. The most frequent suggestions were: - Offer more information. - To offer an honest communication, without technicalities. - Individualizing the IC according to the needs of the patient and family. All suggestions could be grouped into 3 groups: 1- More information: more risk information, benefits, study purposes. Scientific basis for using this drug. Logistical problems in case of participation. Families also suggested changes in the IC model: not only written information, but by other means, the convenience of a CI summary sheet. 2- Better structure and presentation of the IC process, mainly the convenience of sending written information of the CI in advance. They also suggested that the study be explained several times, have time to think about it, and interview in comfortable settings. 3- Suggestions to the doctors who led	Provides opinions of parents and teens on the IC process: Above all, they insist on the need to use all the necessary time in IC, be honest, use more than one session, and be available to parents. We did not collect suggestions from families who refused to enter the clinical trial and could be different from the included group (all families had agreed to participate in the clinical trial).	Qualitative study on opinions of parents and adolescents who have agreed to participate in a phase 1 study. This group has another publication in the review (Miller 2013)	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			N / Not Applicable Toll: Two families	the process. Have a member of the medical team available for any questions that may arise. They also suggested that other non-medical professionals (nurses, chaplains, psychologists, social workers) should be involved in the process.			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Blake 2011	Design: Observational study. Interviews with groups of adolescents with opinions gathered on a text of assent previously read. Recording the interviews. Extraction of dominant themes. Goals: Establish the degree of understanding of the basics of a model of assent Period of realization: does not appear	Number of participants / group: 33 adolescents (16 women, 17 men). Participating Features: Adolescents 15 to 17 years old, healthy, with English proficiency	Intervention: Group reading of a vaccine consent model, and further discussion. Follow-up period: N / Not Applicable Toll: N / Not Applicable	The topics discussed are divided into three groups: 1.- Issues related to a research study: difficulty in differentiating research from clinical practice, difficulty in understanding terms such as "placebo" or "randomization". 2.- Issues related to vaccines: difficulty in understanding how vaccines work (preventive and non-therapeutic use). 3.- Topics related to a hypothetical HIV vaccine: difficulty in understanding the possibility of false positives. Other topics discussed: Need for more information on side effects. Importance of asking for parental consent before or after consent (before the parents in a case of chemotherapy, before the adolescents in a vaccine case).	They verify the importance of insufficient understanding in models of research assent in adolescents	Although the population studied is highly skewed, limitations are found in the understanding of concepts used in research, the need to clarify the difference between research and clinical practice, and the importance of the order between parental informed consent and consent	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Blake 2015	Design: Experimental study. Prospective, randomized, non-blind trial with three groups of participants: with multimedia assent model, with questions and feedback (questions arise during the exposition, and answered before continuing), traditional model of assent with questions and feedback, and model traditional assent, without questions or feedback. After passing one of the models, they answer a questionnaire of 27 questions. Goals: Compare the understanding of assent (traditional model or multimedia model) measured in two ways: average correct answers in the questionnaire, and proportion of participants with a correct response rate greater than 80%. In addition, the rate of correct answers was compared by linear regression with the general school-level test (WRT-4). Period of realization: Not known	Number of participants / group: 120 subjects aged 15-17 years; for each of the three groups (with sample size calculation) was 60 for group with assent on the web, and 30 and 30 for paper assent groups with or without questions. Each group was randomized using a randomization table. Characteristics of the participants: Origin of adolescents from 5 youth service agencies. Inclusion criteria: read and understand English	Intervention experimental group: They passed the web assent program first, then questionnaire and WRT-4. Control group intervention: The other two groups were read the assent model, clarifying doubts (to the subgroup with questions, they passed these). Then they did the questionnaire and WRAT-4. Follow-up period: Not applicable Post-randomization losses: N / Not Applicable	Magnitude of the effect (+ confidence intervals / p value): NO significant differences between groups in the comprehension questionnaire. Adverse effects: Not applicable	The initial hypothesis is not demonstrated, that an electronic model would improve understanding. The authors then analyze secondary aspects of the work	The non-confirmation of the hypothesis could be for several reasons: it is a theoretical model and not a real investigation. Staff who are aware of the classic assent may be different from a team of real-life researchers. They console themselves by saying that the multimedia model is no worse than the classic. In the conclusion do not focus on the important thing and is that the study does not confirm the previous hypothesis, that the electronic assent would be better.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Chappuy 2008	Design: Observational study. Twenty-nine children in a cancer or HIV clinical trial were offered, with parental permission, the opportunity to complete a semi-structured interview to ascertain the understanding of prior informed consent. Goals: Examine children's understanding of informed consent for clinical trials of cancer or HIV. Period of realization: 6 months. It does not indicate date of realization.	Number of participants / group: 29 children interviewed (18 with HIV infection and 11 with cancer), aged between 8.5 and 18 years. 9 of the 29 children had received a diagnosis and proposed IC less than 7 days earlier. Participating Features: Do not	Intervention: The intervention was a semi-directed interview by one of the authors (he did all the interviews) on the 9 aspects that should be included in an IC. This IC was supposed to have been asked for some time to participate in a clinical trial, regardless of whether they had agreed to participate or not. The CI elements that were questioned were: study objectives, study risks, potential self-benefits, benefits for others, procedures, possibility of alternative treatments, duration of participation, right of withdrawal, and voluntariness. A question was asked about each item and 0 or 1 was scored according to the answer. The sum of all the questions was therefore from 0 to 9 (final score). The decision to score 0 or 1 depended on the investigator, according to which he would agree with what was in the IC model.	The understanding of different elements of an IC was measured, the best ones being those referred to: - Objectives of the study - Study Risks - Potential self-benefits. - Benefits for others. The elements with the worst understanding were those referred to: - Procedures - Possibility of alternative treatments - Duration of participation. - Right to withdrawal. - Voluntariness. The information was	We found an incomplete understanding of elements included in an IC for minors. The understanding was related to the age and the time elapsed since the diagnosis. The elements of IC worse understood were those related to autonomy (possibility of alternative treatments, right to withdrawal, and voluntariness). The percentage of patients with adequate response was not high (58-62%), and lower than in other studies; the authors attribute it to the fact that in the latter the diseases at play were more serious than in other	It is not clear when minors are offered the IC document (although in Methods yes it says that the lapse between IC signature and interview, then in Results, does not appear). The interview was oral, and recorded, and the language of the questions adapted to the child's age	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			Follow-up period: N / Not Applicable Toll: N / Not Applicable	considered adequate by 16 children. We correlated the understanding with age, with the existence of a time between diagnosis and application of IC. It does not say the average score of the entire population studied.	studies.		

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Coors 2016	Design: An experimental, prospective, with controls study that analyzes the understanding of the risks of a biobank with an improved IC model versus a standard one. For the realization of the improved IC model, a previous stage of analysis and quantification of the current risks of a biobank Goals: To determine whether improved Informed Consent describing the outstanding risks of a biobank increases understanding in adolescents with Substance Use Disorder (DSM-IV),	Number of participants / group: 194, in Step 4 Participating Features: Adolescents with Substance Use Disorder (some with other related pathology such as behavioral disorders) from a university treatment program. This study was offered independently of the proposed inclusion in the biobank. The controls were adolescent of the same sex and	Intervention: 4 stages, each at the end of the previous one. Stage 1: Meeting to identify risks to biobank participants. The following risks were defined: - Current risks: breach of security, genetic discrimination, unknown future uses, sensitive family information, change of opinion in the future, judicial use, uncertainty of benefits. - Future risks: Purchase of biobanks, among others. - Speculative risks: again, related to speculation. With the current risks an improved IC model was made. A 10-question questionnaire with multiple responses was also developed to test the understanding of the risks, and a scale (Visual Analogue Scale, VAS), which measures a characteristic along a continuum (0-100), to measure highlighting the risks. Stage 2: Check whether participants understand risks as a prerequisite to ordering the importance of those risks. Stage 3: study and compare the participants' level of understanding of risks at the beginning of the study. Stage 4: compare a standard IC model for the genomic study with the standard IC model plus the improved	From Stage 2: Most respondents correctly answered the questionnaire (75-95% correct answers) and rated (by VAS) with more than 50% to 7 of the 8 current risks. Stage 3 (baseline understanding of risks): no differences between groups (adolescent patients of healthy adolescents, parents of one another and older adolescents and their siblings). From Stage 4 (comparison of the standard IC	The addition of an improved IC to a standard IC improves understanding in adolescent patients and parents of adolescent patients to the levels of understanding of their controls. It has been observed that quantifying the current risks through VAS allows the improvement of IC models.	Complex article focused on understanding the risks of an IC for a biobank in a particular population, adolescents with substance use disorder. A previous study of the importance they give to the current risks allows to improve the IC for comprehension purposes. The statistic is debatable (repeated t-tests)	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	compared to a standard informed consent model for genomic addiction research. Period of realization: Not known	racial group recruited through an Internet portal (Craiglist) in the areas coming from the cases. Parents of adolescent patients and adolescents old adolescent patients and siblings of adolescent adolescent patients.	model. In Step 2, measuring the importance of risks, the current risk information collected in Stage 1, and subsequently the questionnaire, and the visual scale to assess the importance of each risk (for each risk was considered only if the answers to the questionnaire were correct). The improved IC that was created only took into account the risks with an importance (VAS) greater than 50. In Step 3, baseline understanding of the risks, another independent group of participants (n = 165) were questionnaire without first passing the current risk information collected in Stage 1. In Stage 4, a third independent group of participants completed the questionnaire after receiving the standard IC only, or this plus the IC improved (n = 195). They describe how they calculated the "understanding of risk" through a score. At all stages, subjects were divided into 6 groups: adolescent patients, adolescent controls, parents of patients, parents of controls, former adolescent patients and siblings of former adolescent patients (and for Stage 4, each of the 6 groups were subdivided between those who received only the standard IC format and those who received the standard plus the improved questionnaire, without indicating how many cases in each subgroup). Follow-up period: Do not Toll: N / Not Applicable	format and Improved IC): The standard IC is better understood by adolescent controls than by adolescent patients (p = 0.005). The understanding of standard IC plus improved is the same in adolescent patients as in controls. Improved IC increases understanding in adolescent patients (p = 0.002). Improved IC increases understanding in parents of adolescent patients (p = 0.006) and siblings of older adolescents (p = 0.034)			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Dove 2013	Design: Observational study. Qualitative analysis of thematic content of pediatric informed consent models of academic centers and public bodies of Canada dated between 2008 and 2011. Six emerging issues are analyzed: 1) If the scope of the parental IC allows the consent, dissent or future consent of the child. 2) If the concept of risk and benefit incorporates the social and psychological perspective of the child. 3) Whether the possibility of withdrawal of the	Number of participants / group: 443 Informed Consents analyzed: 7 biobanks 4 of clinical trials 19 of genetic studies 11 longitudinal studies 17 observational studies Participating Features: Not applicable	Intervention: All selected CIs were analyzed using a modified qualitative method of thematic content. The information sought on emerging issues was presented in a table. Follow-up period: N / Not Applicable Toll: N / Not Applicable	1) Aspects related to consent: - 30% use a specific IC, while 42% use a generic IC (leave open the possibility of future uses of collected data / material). - 56% do not raise the possibility of dissent. - 49% do not raise the possibility of an agreement or consent in the future (if the research changes or the majority of the population reaches the age of majority) 2) Risks and benefits: - 26% pose potential risks from a social, psychological or financial point of view. - 67%	Since they were CIs of different types of studies, the variability of formats was expected. Thus, open IC formats are more likely in biobanks, since the samples are stored for a long time. With regard to risks, they remember that they go far beyond physical risks, and that Canadian law requires them to be taken into account. They also refer to research with more than "minimum risks", and therefore have to take into account all types of risks. Regarding the information of both the results of the study and of incidental findings, there is no consensus, especially in relation to genetic studies and biobanks. Limitations of the study: The study does	Study of IC models seeking to detect emerging problems of current IC models. They find many improveable aspects, which describe them in a table: Best practices for drafting paediatric research consent forms in Canada Emerging issue Best practices Scope of parental consent Broad consent · The possibility of future, unspecified research uses should be mentioned prior to obtaining consent and the consent form should be worded accordingly. When the child is considered to be legally able to provide consent, consent should be renewed, if feasible. · Where feasible, data and / or samples should be coded (not anonymised) in order to allow researchers to maintain contact with the child. Ability to dissent · The possibility of a child's right to dissent, provided there is an ability to understand the significance of research or his / her role in it, should be disclosed. Financial, social, and psychological issues · Consideration of potential harms must include physical as well as psychological, social or financial harms. Cumulative harms considered in assessing	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	child is respected and to what extent withdrawal is permitted. 4) Whether the information from the research results includes individual results and incidental findings. 5) If doubts about privacy and confidentiality are resolved from the perspective of the minor and if the data are correctly identified. 6) If custody and access to biological samples and data of the child are properly treated. Goals: 1) Analyze how much information on			consider indirect benefits 3) Extension of withdrawal: - 65% name the possibility of the child withdrawing from the study. - The way of doing the withdrawal (destruction of data, samples, etc.) is only mentioned in 35%. - No CI mentions how to handle a possible disagreement between parent and child regarding withdrawal. 4) Information on results and incidental findings: - This figure is not mentioned in 40% of ICs. Of those who mention the return of data, some offer	not focus on the understanding of IQs but rather on emerging ethical aspects (which I believe belong to the scope of information that should be included in the IC). There is no representation of CI models for qualitative research, nor for community research.	individual harms · Cumulative harms should be considered. How? Benefit? is characterized · Risks and benefits should be considered from the child? S perspective. Withdrawal Ability for withdrawal The child's ability to withdraw should be explicitly disclosed, as well as any circumstances that might limit the ability (eg if immediate withdrawal could harm the child). Extent of withdrawal · The extent of the ability to withdraw should be explicitly disclosed (eg if data and / or samples are anonymised, the consent form should state that withdrawal is not feasible). Informational entanglement · The potential for a child and parents to disagree about whether to withdraw, and its potential impact on the research project, should be described. Return of research results and incidental findings The potential and process for returning research findings and incidental findings · The potential for disclosure of research findings and incidental findings, as well as its process (including disclosures and the possibility for entitlement to non-disclosure), should be described. Individual findings and incidental findings that have clinical significance should be communicated to the child and / or parents when either prevention or treatment is available during	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	emerging issues is found in the CI sample analyzed. 2) Evaluate the quality of that information using a structured list based on best practices. 3) Proposal of improvements for the development of IC in minors. Period of realization: 2011			it individual and others, aggregates. 5) Privacy and confidentiality: -All ICs refer to the right of parents to access information of the child (but do not refer to the right of children to limit it). - Identification is unspecifically protected in 33% of cases, coded in 58% (ideally), and anonymised in 9% of ICs. 6) Custody and access of data / samples: - 42% of ICs referred to specific time periods of data / sample custody. 21% made no reference to this aspect. - 47% did not refer		childhood, and with adequate counseling provided. The interconnected nature of the potential risks and benefits of such communication should be disclosed. Duty to receive information · Parents should be aware that they will receive clinically significant information about conditions that are preventable or treatable during childhood. Privacy and confidentiality Parents? right to access information regarding their child · In research projects that collect and use particularly sensitive information, such as pregnancy status, drug use, or sexual history, consent forms should disclose what information will and will not be communicated to parents, and which information disclosure requires the child? S consent. Nomenclature for data / sample identifiability · Standardized sample identifiability terminology should be used: coded (including single-coded and double-coded), anonymised, and anonymous. · Biobanking or genetic research consent forms should state that anonymised or coded data and samples can not guarantee privacy. Retention of and access to data / samples Retention period (s) of data / samples · Consent forms should clearly distinguish between what is a legally required data / sample retention period and a retention period decided upon by the researcher. Access to data / samples	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
				to possible transfers of samples / data to other locations. 40% said they could do so in the future.		· The policies and procedures for access to data and / or samples should be disclosed. · These policies and procedures should consider the privacy impact (both to the parents and child) of access to coded or anonymised information, including: organizational safeguards, technological measures, physical measures, and ethics oversight. · If feasible, researchers should disclose a method for listing all approved projects that are accessing the data and / or samples.	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Espejo 2011	Design: Observational study, with three stages: to elaborate a scale of evaluation of the moral development for adolescents according to the stages of Kolhberg, evaluation of this scale comparing it with a already validated test (DIT test of James Rest), and comparison with the subjective average of the tutors of the cognitive ability and maturity of their students. Goals: Have a practical tool to assess the degree of moral development according to Kolhberg stadiums Period of realization: not applicable	Number of participants / group: 60 Participating Features: N / Not Applicable	Intervention: Elaboration of the scale. Application to 60 adolescents aged 14-15 years, together with the DIT scale, and subjective assessment of the tutor Follow-up period: N / Not Applicable Toll: N / Not Applicable	Poor correlation between the three variables	N / Not Applicable	Does not seem useful for the I-Consent study	Not classifiable

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Fisher 2016	Design: Observational study of the responses in groups of discussion of adolescents of sexual orientation minorities to questions related to a hypothetical study on prophylaxis pre-exposure to HIV. Goals: - Be able to inform the local Clinical Trials Committees that there is capacity in these children to make informed self-consent. - Effect of the need for parental leave to make the decision to participate in such a study. - Attitudes about understanding the purpose of the study, risks and benefits, adherence and randomization. Study if young people are empowered to raise doubts and	Number of participants / group: 60 adolescents aged 14-17 Participating Features: Sexual relations with men, HIV negative, Internet access, and domicile in USA	Intervention: Six groups were stratified by age, sex, and parental attitude towards their sexual identity, and the identities of the debate were anonymised. Sequential information and questions were sent to each group. Then a video was offered with information from the hypothetical study. An open questionnaire was made on the video, and the researchers planted several issues for discussion: paternal leave, randomization, privacy, and adherence to medication. Standardized information was extracted from the discussion groups for analysis. Follow-up period: N / Not Applicable	It only gives numeric data. Faced with the question of the need for parental leave, most answered that in that case he would not participate. There was an acceptable understanding of the risks and benefits of the study, of the need for daily adherence to treatment. There was a reasonable understanding of the need to know the study because it would be proposed that out of informed self-consent.	They meet the objective of demonstrating that young people aged 14 to 17 years of sexual minorities (almost all homosexuals and a few transgender) were able to understand the characteristics of a study of HIV pre-exposure prophylaxis, with a view to proposing to the Test Committees Clinical the possibility of informed consent.	Article with objectives different from those of the I-Consent. It could serve as an example of the need for consent in minors to specific problems	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	consent voluntarily. - Study your ability for a responsible CI. Period of realization: 2015		Toll: N / Not Applicable				

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Friedman 2016	Design: A randomized, prospective, randomized, three-arm, non-blind, experimental study conducted during a larger study to find out the behavior of young gay men on the Internet. Recruitment by Facebook. Goals: Study whether young, gay-oriented 14-17-year-old males improve their understanding of an online assent model by reinforcing with questions during the assent process. Period of realization:	Number of participants / group: Recruited 623 subjects. Excluded during the process 121 subjects. Final Groups: Group 1 (reading of assent): 158. Group 2 (reading of assent with 2 questions about him): 126 subjects. Group 3 (reading of assent with 7 questions about him): 114 subjects	Intervention experimental group: Group 1) Reading the document of assent and subsequent desire to participate. Group 2) Reading of the document of assent and answer to two questions about voluntariness and risks, and later desire to participate. Group 3) Reading of the document of assent and answer to a questionnaire of 7 questions (the previous two and 5 more) on the process of assent, and subsequent desire to participate. At the end of the study, the two questions from Group 2 Control group intervention: Yes	Magnitude of the effect (+ confidence intervals / p value): The probability that the subjects in groups 2 and 3 correctly answered the two questions when they were questioned at the end of the study was of an OR between 3 and 10, compared to those in group 1. They do not say how much time passed between the first questionnaire and the second Adverse effects: N / Not Applicable	The addition of two questions about test risks and trial voluntariness, made during the assent process, improves understanding of the test (measured by correct answer of those same two questions at the end of the study, versus controls). This improvement of understanding is in exchange for more losses during the process of assent, if the subject is asked for a more active effort (answering the questions). Conclusion: If a computer support is used for an assent in which information is proposed with a more active interaction with the subject, understanding would be improved, but a way of not sacrificing the possibility of more losses would be sought (by that effort extra that the subject is requested).	He is interested in the demonstration that the more difficult the process, the more withdrawn, but that a very simple interactive consent process improves understanding	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	Not known	Characteristics of the participants: Partially	Follow-up period: N / Not Applicable Post-randomization losses: 27 in group 1, 61 in group 2, 81 in group 3				

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Giesbertz 2016	Design: Theoretical study Goals: It tries to answer the question how should the content and the consent process be to be considered a personalized assent, in the case of biobanks Period of realization: not applicable	Number of participants / group: N / Not Applicable Participating Features: N / Not Applicable	Intervention: N / Not Applicable Follow-up period: N / Not Applicable Toll: N / Not Applicable	1. Content of assent: - Information to be provided. - The information must be individualized - The information begins with specific aspects - Give more information at the request of the child. 2. Assent Process: - How to offer the information? Classic methods (personalized document and interview), plus information technologies -Adult's role. The parents modulate and help to a process in which the author gives great autonomy to the child: he does not see the assent as mere confirmation. - The assent itself: Verbal communication and information. Check that the child understands, wants to know,	Although assent will not always be obtained (children with little maturity, who reject, etc.), it must be actively sought, because it shows respect for the child, improves the quality of the biobank, and improves the child's commitment for future reconstitutions. Take into account the complexity of the biobank when insisting or not on the assent. The content and process of the biobank must be known to the local clinical trials committee. The process of assent must be flexible. See the custom assent as a commitment search.	It defends a vision of the assent in which the decision of the child is a priority, in front of alternative conceptions in which the assent is only the confirmation of the previous decision of the parents.	Unclasificable

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
				and wants to decide. - Subjectivity of assent: the process can be modified by the researcher's own action. - Reaction of the child. How to interpret silence, as assent or as dissent?			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Grootens 2015	Design: Observational study with intervention. Goals: Development and test of a comic to explain aspects of the IC. Period of realization: does not appear	Number of participants / group: All students in 4 classrooms between 10 and 14 years old. N = 101 children aged 10-14 years. Participating Features: Do not	Intervention: Design of the comic by a cartoonist and a communicator, without the participation of minors. We moved to 4 classrooms for children from 10 to 14 years. Subsequently a questionnaire was made with open and closed questions. Then, a group questionnaire with open questions about the comic and its opinion of the process. Follow-up period: Do not Toll: Do not	Acceptable comprehension (greater than 65%) in the 8 basic areas of research (voluntary, ineffective drug, withdrawal, randomization, placebo, side effects, anonymity, benefit uncertainty). Children were satisfied with the format	A comic format can increase the understanding of an IC for a clinical trial in minors.	The use of simple and attractive methodologies for children can achieve acceptable understanding of the most relevant aspects of clinical research.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Hein 2012	Design: The article is the project description: it is a prospective cohort study that compares the competence through a professional assessment, with the MacCAT-CR instrument. Goals: - To study the reproducibility of the MacCAT-CR to assess the competence of children in the CI of clinical trials. - To establish a reference standard from the MacCAT-CR score. - To estimate age limits of competence Period of realization: does not appear	Number of participants / group: 160 Participating Features: Patients between 6 and 18 years old recruited from three Dutch hospitals to propose to participate in different clinical trials. The projects to be proposed were oncology, pneumology and pediatric ophthalmology	Intervention: The MacCAT-CR is compared with the subjective assessment of the baseline clinical investigator, and two experts who judge yes / no on the basis of the interview accompanying the Informed Consent request of the baseline clinical trial. The authors translate the MacCAT-CR, adding two questions: What do you think your parents will think about whether or not you take part in the study? And your friends ?, and With this they try to complete the consequences of social relations. Measurements: - MacCAT-CR: total score, score of the different domains, and binary (yes / no) with respect to the competition. - Wechsler Nonverbal Scale of Ability (WNV) to determine intelligence. Statistic analysis: - Reliability (accuracy) of the MacCAT-CR test.	THIS ARTICLE IS ONLY THE PROJECT. NO RESULTS	This would be the first empirical study at world level that seeks to establish a standard combined with the validation of a measuring instrument.	This article is only the research project. A validated tool is used in adults to determine competence to consent to a research project, and is adapted for children (MacCAT-CR). The resulting tool will be passed to a sample of 160 children who are proposed to participate in different trials clinical trials. Competition as measured by MacCAT-CR will be compared to the judgment of the investigators by interviewing the subjects. Description of the MacCAT-CR: semi-structured interview that measures the 4 aspects to be evaluated in the determination of the competence of a subject: - Understanding information. - Reasoning in the	Unclassifiable

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			- Validity of the MacCAT-CR test in relation to the reference standard. - Interobserver reproducibility of the different tools used (MacCAT-CR reference standard test). Follow-up period: N / Not Applicable Toll: N / Not Applicable			decision-making process. - Appreciation of the effects of participation in the subject. - Expression of an election about that participation. Two parts on the test: 15-20 minute interview, and classification. The authors describe what factors are child-specific to make a judgment of competence: factors related to aspects of development (abstract thinking, cognitive social aspects, changing circumstances for child development, etc.), provision of information (adapted to age of the child, in small blocks, with multimedia support ...), and systemic influences (of parents, friends, and professionals).	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Hein 2014	Design: Observational study. Patients 6-18 years of age who participated in several clinical trials or observational studies, and who were given the MacCAT-CR test that examines competence for assent. Prospective study. Goals: To test a standardized test of competence (MAcCAT-CR test) as to its reliability and validity, and to estimate age cuts to assume competence in assent Period of realization: 01 / 2012-01 / 2014	Number of participants / group: 161 study patients, with different participation rates. Participating Features: Partially Described	Intervention: Application of the MacCAT-CR competence test, modified by the authors for use in children. Comparison with a competency assessment performed by clinical assessment, through a filmed interview, and analyzed later, blind to the results of the competition test. From this analysis of the recording, each researcher spoke about the competition (in 4 categories, most likely competent, probably competent, probably incompetent, and most likely incompetent). This assessment was the reference on which the MacCAT-CR test was measured Follow-up period: N / Not Applicable Toll: N / Not Applicable	Reproducibility and validity of the MacCAT-CR test for children: good (intraclass correlation coefficient between 0.68 and 0.92) Unidimensionality of the confirmed test (confirms the utility of the global test to determine competence, because each of the 4 components are related). Good agreement between the MacCAT-CR test and the standard to assess competition Value of the MacCAT-CR test to determine proficiency, greater than or equal to 35 points. Age cut off points for competition: 11.5 years (with limits of 9.6-11.2 years with 90% sensitivity and 90% specificity respectively)	The modified version of the MacCAT-CR test is accurate to determine competence in assenting in clinical research in minors, suggesting ages of use. Thus, under 9.6 years the child is likely to be incompetent, and over 11.2 years, it is likely to be competent. They suggest that in the period between the two, the test can be used to determine the child's competence.	This study shows age limits in which the competence to assent in minors is expected or not. Between 9.6 years (limit of incompetence) and 11.2 years (limit of competence) the proposed test could be used to define it individually.	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Hein 2015 a	Design: Observational study. It is complementary to that of Hein 2014, which analyzes, with the same data from that study, the potential factors that determine the competence of the child for consent to research, and to what extent these factors explain the variation in competition judgments. Prospective study, case series, which analyzes the explanatory variables of the existence of competence to make Informed Consent in minors. Goals: Analyze, with the same data from the Hein 2014 study, the potential factors that determine the child's competence for consent to research, and to what extent these factors explain the variation in	Number of participants / group: 161participants Participating Features: Participants from different clinical trials with different complexity and risk	Intervention: The competition was established exclusively by the MacCAT-CR test (dichotomous result, "competent" or "not competent"). The variables studied in relation to the competition were: Determining, "causal" variables: Age, sex, IQ, experience with disease, socioeconomic status, and ethnicity. Contextual variables (complexity of the decision, risk of the decision, paternal judgment on the competence of the minor and decision to participate by the minor). Statistical method: logistic regression. Contextual variables were analyzed after creating the best model.	- Association of variables with competence: all variables except sex, and experience with the disease were positively associated with competition according to the MacCAT-CR test. - Contribution of the different variables to the competition: only the age explained 56.4% of the variance. Age and Intellectual Coefficients accounted for 69.1% of the variance. The remaining variables (including the contextual ones) explained the 5.4% of the variance.	Age and IQ are the main explanatory variables for the presence of juvenile competition, measured using the MacCAT-CR test. The experience of the disease is not, according to this study, an important variable that determines the competence. Although in isolation the parental assessment of the competition is associated with competition according to the MacCAT-CR test, this assessment hardly contributes to the overall model. The authors recognize a limitation of having combined studies of high, medium and low risk and complexity (which in any case are quite subjective variables).	This study quantifies the importance of different variables in the measurement of children's ability to consent to research: Age and IQ are the most important factors. Age can be generalized and influence future social or legal changes in relation to the autonomy of the child, but the IQ would require a much more personalized assessment.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	competition judgments. Period of realization: not applicable		Follow-up period: N / Not Applicable Toll: N / Not Applicable				

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	QUALITY OF EVIDENCE
Short quotation: Hein 2015 b	Design: Publication of comments on the work of Hein 2014 Goals: Not listed Period of realization: not applicable	Number of participants / group: Not applicable Participating Features: Not applicable	Intervention: Not applicable Follow-up period: Not applicable Toll: Not applicable	They differentiate two concepts: "capacity in decision making" to refer to the different levels of skills of the patient, and "competence", to refer to the degree of ability that a patient has to be able to make autonomous decisions. They insist on the need for empirical data and comment on the results of the application of a tool (the MacCAT-CR) to 161 children. From the results, they theorize. This tool analyzes the 4 aspects that measure the decision-making capacity that reflect competence standards: - Understanding of information. - Reasoning in the decision-making process. - Perception of the effects of that participation in the patient. Expression of an election about participation. It is a semi-structured interview that seems complex. It is known from the outset that in this test the four components are usually parallel in children, and independent in adults. When applied to a group of children, they find that there are two limits, 11.2 to define a child as competent, and 9.6, to define it as incompetent (with a gray area in the middle). They also find that competition does not vary for different severity of the clinical decision. With this data they are considered if the method of IC by the adult and assent in the child is the best method (on the one hand it leaves behind a demonstrated competence, and on the other, they have doubts about if they have escaped some aspect important to condition the validity of that result, still for another, these ages collide with the legislation of most countries). Ethical	The authors analyze the results of their own previous publication (Hein 2014) using a tool (MacArthur Competence Assessment Tools for Clinical Research, MacCAT-CR) to see from what age children would be competent for informed consent in clinical research . In this article they marked two limits: 11.2 to define a child as competent, and 9.6, to define it as incompetent (with a gray area in the middle). From the definition of normative judgment of competence: a child would be considered competent or well In spite of this they propose a selective implementation of the IC based on case by case and not by age, and, secondly, a dual IC. Authors' recommendations: - They do not recommend a selection on a case-by-case basis, but rather spend the age limits that they find in their work to request ICs for children (ie, over 11.2 years, the competent entry child would be considered) Cultural differences must be taken into account. Already in another point of the article they say that the CI to minors varies a lot between countries, being the one of accepting of smaller age the own Holland (its country), with twelve years, whereas the USA or would have of the majority of legal age (18 years). They therefore propose a dual consent, assuming the risk of a discrepancy between parents and minor. This dual consent would have two parts, one for parents and one for the child. Unresolved issues: - Until what age should dual consent be given? 16.18 years? - Extending those capacities to other areas of the	Unclassificable

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	QUALITY OF EVIDENCE
				aspects: This instrument has a problem. It does not measure emotional competence. Another problem is the possible change of values in the child that could affect his consent. Legal aspects: What is considered before conflicts with legality, which sets ages for competition. It would then establish the debate as to whether competition should be analyzed on a case by case basis, or presupposed according to the child's age. In relation to the best interest of the child, the authors suggest that if the child is able to overcome the items in the questionnaire, then he can give IC, and this, in turn, means that he is acting in his best interest. Developmental Aspects: Unlike adults, who are considered competent unless proven otherwise, children are considered entry incompetent. According to their study, the specificity to identify competence in children aged 11.2 years and over was 90%. In relation to who sees the most competent child, whether parents or professionals, literature is discordant, although it seems to predominate the view that parents assign more competence to children than professionals (perhaps because parents see it from an integrated point of view in the family, while professionals see it more from an independent point of view). to manage the impulsivity and the lack of vision of long-term consequences typical of the adolescent? There is no response at this time. On the other hand, there is agreement to consider the parents necessary for the development of a possible participation of a minor in an investigation (from creating the right environment to solving logistical problems)	public's life of the minor, such as civil, criminal, etc. - Need for more studies of MacCAT-CR to minors. - Need for more neurofunctional studies.	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Hunter 2007	Design: Theoretical Goals: Personal comments on the possibility of using the Gillick competition in research Period of realization: ns	Number of participants / group: Ns Participating Features: Ns	Intervention: Ns Follow-up period: Ns Toll: Ns	The Gillick competence assumes the maturity and ability to give informed consent on the part of a child under 16 years if the attending physician appreciates that it can be considered competent. This situation would be relatively clear in clinical practice but its application in research would be more doubtful. The researcher may not have the necessary skills to estimate the competence of a minor, and may also have a personal interest in research, in this case, when recruiting. The authors suggest that the Gillick competition should not be applied in research, since there may not prevail neither the non-maleficence nor the beneficence, and therefore not seek the best interest of the child, although there is an apparent respect for their autonomy. On the other hand, if it were applied in the investigation, we would give more priority to the autonomy of the child when making the decision, than in a possible beneficence or non-maleficence. According to the authors, if the Gillick competition were applied, there would be a possible collision between respecting the hypothetical rights of the minor to participate in an investigation and the possibility of causing harm. In two situations the Gillick standard could be used in research: when the investigation offers likely benefits to the participants, with few risks. The second, more debatable situation would be when the requirement of parental consent could threaten very important investigations. In this case the competition Gillick competition should be verified by non-research subjects.	In principle it does not interest for the systematic review. But somewhere there will have to introduce the issue of what is "minimum risk" in juvenile research	Unclassificable

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: John 2008	Design: Observational study, on the opinion of parents and minors regarding blood extraction, in a previous research on a vaccine Goals: Establish the relevance of asking healthy children to make a decision about their participation in an investigation. Period of realization: 02 / 2005-08 / 2005	Number of participants / group: 73 children and their parents, from an initial sample of 300 children who were included in the vaccine study Participating Features: Healthy children who had participated in a study of a vaccine started three years earlier.	Intervention: Intervention done on the day of the visit for blood collection for serology. The children were asked if they knew what they were going to that day for the consultation. The children were informed about the study of vaccines and about what they were proposed: to make a blood extraction for serology), with risks, advantages and disadvantages. Verbal assent was granted. Previously the parents had signed a formal consent. After the blood was drawn, the children were given a questionnaire to establish understanding about the vaccine study. Parents were given a questionnaire about their opinion regarding children's understanding of the study. Follow-up period: Do not Toll:nN / Not Applicable	71% knew they were going to have a blood test. More than half did not know why they were going to do the analysis. After the explanation and extraction, a questionnaire was made: 33% still did not respond or that the analysis had been done, although 29% answered that it was to see protection against a disease. 65/73 understood that they could withdraw from the study. The questionnaire to the parents showed that the opinion of the minor should be respected although some had previously proposed a persuasion. 75% thought that the decision to participate was exclusive to the parents.	Most children aged 6-8 are not able to understand the factors surrounding a research study, with marked individual differences. Discusses practical aspects to assess dissent by the child, which they propose must always be respected. They believe that the information to the child should be through the parents.	Study with unclear objectives, confusing methodology and non-concrete results (especially opinions).	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Koelch 2009	Design: A feasibility article on the use of MacCAT-CR in children with ADHD or ADHD plus challenging disorder who were asked to participate in a clinical trial or open study to study the understanding of such investigations. Goals: Explore the feasibility of providing research information for informed consent and how it is understood by children and parents Period of realization: Not applicable	Number of participants / group: N / Not Applicable Participating Features: 19 minors from the two studies were selected (does not say selection criteria	Intervention: The MacCAT-CR test was used in minors and in parents separately. The children were also measured the IQ. Parental socioeconomic status was collected. Interviews to make the MacCAT -CR were recorded and then analyzed by two psychologists. A qualitative content analysis of these interviews was done, and an assessment of the parts of the MacCAT-CR. Follow-up period: Do not Toll: N / Not Applicable	-Comprehension: The issues related to the development of the study and the advantages, disadvantages and risks of the study were well understood. The primary purpose of an investigation was not well understood (it was thought to be the child's personal benefit). The concepts of placebo and randomization were not well understood. The concept of voluntary retreat without consequences was well understood. - Appreciation: Minors misunderstand what they have been proposed for in the study. Most thought it was to see if the medication could help them. They also thought they were not going to get a placebo. - Reasoning (reasons to accept or refuse to participate). Reasons to accept: hope for improvement, comfort (in the long-acting methylphenidate study), desire for exploratory behavior (try a new drug). Reasons for rejection: invasive procedures in the study, changes in the therapeutic group, and time expenditure.	The more abstract themes (primary objective of a clinical trial, randomization, and the nature of placebo) are misunderstood (often also by parents).	Exploratory and narrative study based on interviews	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	QUALITY OF EVIDENCE
Short quotation: Koelch 2010	Design: Observational, pilot study to see the utility of the MacCAT test for the understanding of informed consent in a sample of 12 children with ADHD and oppositional defiant disorder (DSM-IV) and in their parents. Goals: - To study the usefulness of MacCAT-CR in a population of children with ADHD plus oppositional defiant disorder to determine their ability to consent to participate in a clinical trial (atomoxetine vs placebo trial) - To compare possible differences in competence using the MacCAT test -CR between patients and parents. Period of realization: Not known	Number of participants / group: 12 minors, and 12 progenitors Participating Features: Children diagnosed with ADHD and oppositional defiant disorder according to DSM-IV criteria	Intervention: 1.- Written information about the clinical trial provided 24 hours before the intervention. 2.- Clinical evaluation of an investigator on the competence of minors and parents for consent. 3.- Administration of the MacCAT-CR test separately to minors and parents. The interviews were recorded. Different professionals did the interview and valued the recordings to rate them. The score of the recordings were made by two independent psychologists, separately in the 4 areas according to the following score: - Understand information about the research project (5 subareas, each scored from 0 to 2) - Reason about potential risks and benefits of the choice made (3 subareas, each scored from 0 to 2) - Appreciate the nature of the election as well as the consequences of the election (3 subareas, each scored from 0 to 2). - Express a choice (1 subarea, scored 0 to 2). 4.- The agreement between professionals who made the scores was determined by intraclass correlations. 5- Other determinations: CI to the minors and	- Clinical evaluation of the competition: all the minors and the parents were valued as competent. -Valoración of the test of MacCAT-CR: - Concorporation between professionals: excellent for the recordings of the minors (0.94-0.95), acceptable for those of the parents (0.7-0.83). - MacCAT-CR test scores for each of the sub-groups (minors vs. parents): Comprehension: 5.86 vs. 9.08 (for a maximum score of 10). Appreciation: 2.64 vs 4.96 (for a maximum score of 6). Reasoning 3.05 vs 4.63 (for a maximum score of 6). Expression of an election 1.77 vs 1.88 (for a maximum score of 2). Minors scored lower than parents. - Correlation with IQ: no	Pilot study given the small number of patients. Little agreement between a clinical assessment and the test result among the minors. Parents have better understanding than minors.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	QUALITY OF EVIDENCE
			socioeconomic status of the parents. Follow-up period: Do not Toll: N / Not Applicable	correlation. There was better understanding in parents than in minors. Some items were especially difficult: purpose of the study, nature of the placebo, possible lack of benefit for the patient.		

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Kupunen 2012	Design: Observational study evaluating two tools to obtain the assent of children in a study on food problems in children receiving chemo (Food Study). Design of the storyboard and the soup of letters: Graphic storyboard (for children 4 to 6 years): Children fill with drawings (stickers?) the gaps of a graphic story related to the project. Letter soup: a soup of letters with terms like "study", "participation", etc., and after discovering them, and making it clear that it is a game, you are invited to participate in what the game says, a study research. If they agreed to participate, a signal of withdrawal (verbal or non-verbal) was agreed. Goals: Analyze child-centered techniques to see usefulness in the process of assenting in research. Period of realization: Not known	Number of participants / group: 14 children from 29 families who were participating in the Food Study. Participating Features: Do not	Intervention: Each child was offered one of two methods: 6 chose the soup of letters, 6, the graphic history, and 2, 10 and 12 years, a direct discussion. Evaluation by means of a thematic analysis of the field notes taken during the process, and analyzed by two independent researchers Follow-up period: Do not Toll: N / Not Applicable	Five topics were discussed: 1.- Introduce the assent as a game. 2.- Adopt a style of communication that will empower the child. 3.- Avoid distractions during the process, especially clinical interruptions. 4.- Take advantage of moments of concentration of the child. 5.- Ensure voluntary.	The use of study-centered techniques allows for a process of assent in young children (up to 5 years old).	Description of child-centered methods that allow for their empowerment when applying for assent.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Lally 2014	Design: An experimental study in which a double message information technique (the message starts with frequent error information, along with the correct answer) improves the understanding of the concepts of placebo and randomization of an informed consent for a hypothetical study of HIV vaccine in adolescents. Three branches: basic IC information, an explanatory brochure with simple messages (presentation of factual facts associated with participation in the clinical trial), and an explanatory brochure with double messages (presentation of an erroneous concept refuted with factual information). Goals: Evaluate supplemental educational brochures designed to increase awareness in a clinical trial of an HIV vaccine through a persuasive message, focusing on those aspects that may be central to preventive misinterpretation. Investigate the possible association between understanding specific aspects of that clinical trial (randomization, untested efficacy, and interpretation of adverse effects) with impulsivity, health knowledge, and knowledge. basic math .	Number of participants / group: 120 16-19 year olds from 4 sites participating in the ATN project. Participating Features: 120 16-19 year olds from 4 sites participating in the ATN project. Inclusion criteria. Sexually active with men, and desire to participate in a clinical trial of these characteristics	Intervention: After signing the IC for this study they were given a questionnaire (IAQ part 1) (Interviewer Administered Questionnaire). The IAQ is a questionnaire that measures reading and math skills, impulsiveness, interest, and demographics. After completing this test they were all passed on to the pretended CI for a clinical trial on HIV vaccine. After him, he was randomized into three groups. The first, without supplementary information. The second, with a booklet with simple messages, and the third, with a booklet with double messages. Later they filled out the IAQ Part 2 with 10 questions that had to be answered with Likert responses (5 responses, from totally agree to totally disagree). There were also three questions about the desire to participate. Follow-up period: N / Not Applicable	Better understanding of the aspects of randomization and side effects by means of an ANOVA test between the group with supplementary information of double messages and the control group (only CI), but no less understanding in the aspect referred to the unproven efficacy. Regarding the second objective, it was found that there was better understanding with better literality.	There is a better understanding with the use of a double message booklet. The use of explanatory booklets with double messages does not compromise the desire to participate (whereas the use of a brochure with simple messages diminished the desire to participate)	The methodology (double message explanatory booklet) is interested in improving understanding	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	Period of realization: Not known		Toll: N / Not Applicable				

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Murphy 2007	Design: A randomized, open trial to study the understanding of two models of informed consent for a hypothetical HIV vaccine in adolescents Goals: -Develop a simplified model, with images, friendly to adolescents, of an IC model already tested in HIV vaccine studies (prototype HIVNET) .- Test this simplified model in groups of adolescents at risk.- Conduct a clinical trial among adolescents at risk of HIV to compare this simplified model with the standard, and see their degree of immediate understanding. Period of realization: November 2003-May 2004	Number of participants / group: 263 subjects recruited. 187 completed the study (94 with standard IC and 93 with simplified). Characteristics of the participants: Origin, gender, race, sexual orientation	Intervention experimental group: Random assignment to standard or simplified format. Out loud reading. Video recording. After reading the ICs, the following tests were passed: - understanding. 19 questions with multiple answers (3 answers) (provides definitions of questions). - memory of questions. 3 open questions about benefits, risks and experience of the visit - of willingness to participate: a question, if you did the study tomorrow, would you participate? - on HIV- cognitive measures, through two intelligence tests (K-BIT and WJ-R). Control group intervention: the same Follow-up period: N / Not Applicable Post-randomization losses: Do not	Magnitude of the effect (+ confidence intervals / p value): The comprehension score (19 questions) was better in the group with the simplified CI format than with the standard (median scores of 16 and 14, with maximum possible of 19; p = 0.0005). In a multivariate model the variables associated with a better understanding were the C Intelligence, the type of IC and the place of the study. Adverse effects: N / Not Applicable	The improvement of the simplified CI does not know if it is by the addition of illustrations, by the simplified text, or by both.	Given the characteristics of the study, the items best and worst understood are the peculiar ones of the study, and the important thing is the improvement of the global understanding by simplifying and illustrating the IC model	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Nelson 2016	Design: Observational study with intervention Goals: Adapt the MacCat-CR test to adolescents. To verify with that test the capacity for consent for research in healthy adolescents. Examine developmental variables that influence the ability to consent to research. Period of realization: Not known	Number of participants / group: 30 adolescents 14-21 years old coming from adolescent clinics and community centers. Participating Features: Do not	Intervention: - Collection of demographic data. - Realization of the REALM (Rapid Estimate of Adult Literacy in Medicine) test. - Reading of three models of informed consent for three hypothetical studies. - Performing the MacCAT-CR test (performed during the IC process, not after the IC process, as in adults): 23 questions that are evaluated according to the level of correction in the response, in 0.1, or 2. - Classification through FAS II (Family Affluence Scale) of the socioeconomic level. Follow-up period: N / Not Applicable Toll: N / Not Applicable	30 adolescents (24 women and 6 men) between 14 and 21 years. Acceptable ability of the whole group (even the youngest had a capacity similar to that of adults). They found association of age, literacy and socioeconomic status in the three subsections of MacCAT-CR (understanding, appreciation, and reasoning). Aspects with worse understanding: that a clinical trial, in addition to effectiveness measures safety, and how to withdraw of a study.	The MacCAT-CR test, as adapted, is useful for measuring ability in adolescents, and is able to discriminate variables that influence their outcome such as age, literacy, and socioeconomic status.	Pilot study of the applicability of the MacCAT-CR test to healthy adolescents	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Ott 2016	Design: Observational study with intervention. Goals: To study the understanding of an IC against a hypothetical HIV vaccine, focusing on one aspect, the interpretive bias of IC that the adolescent can do, thinking that there is more probability of falling into the experimental branch, that this will be more effective, and that in this way unsafe sex will not be so risky. Period of realization: Not applicable	Number of participants / group: 33 participants aged 16-19 Participating Features: Adolescents of both sexes of 16-19 years, HIV negative and with sexual activity with men, and with desire to participate. Recruitment in clinics, youth agencies and youth programs.	Intervention: Assent of the minor without paternal consent. After reading an IC for a hypothetical HIV vaccine and a supplemental material on what is a clinical trial, and after participating in a questionnaire accepting that hypothetical investigation, a qualitative individual semi-structured interview was conducted for 30-60 minutes. Interviews recorded. Analysis of the interviews through a method based on grounded theory. Follow-up period: N / Not Applicable Toll: N / Not Applicable	5 essential aspects to be analyzed in a clinical trial on vaccines: - Understanding how vaccines work. Incomplete understanding that a vaccine is preventive, non-curative, and not 100% effective. - Understanding what an experiment is. It was generally understood, in the sense that it was verbalized that the vaccine might not be effective. - Understanding what a placebo is. Overall, it was well understood, although one participant confused placebo with a placebo effect. Doubts as to the logic of using placebo. - Understanding what is randomization. Incomplete comprehension (only acceptable in 22 out of 33). In general, they included their own luck in the randomization process. - Understanding the need to maintain safe sex. In general, good understanding.	Adolescents were active in the IC information process. Interviews facilitated this understanding, clarifying concepts and providing feedback. The theoretical risk of unprotected sex bias from feeling the adolescent protected by the study process was not met in interviews. The authors acknowledge that a study of this type is difficult to generalize.	Low quality for poor reproducibility.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Lee, 2013	Design: Experimental, analytical study of intervention. Goals: - Evaluate the understanding of a simplified IC document, with a questionnaire of 6 questions V / F (available in English and Spanish), in possible participants of a clinical trial with Hepatitis B vaccines. - Evaluate the educational intervention of the researcher, on the improvement of the understanding of the information. Period of realization: It is not explicit	Number of participants / group: n = 123 young people aged 12-17 years Participating Features: Age	Intervention: An IC document was improved and simplified. This modification was reviewed and approved by a panel of ethical experts (Office of Human Research Protection), in order not to lose content. Readability: 6th grade + plain language + graphics that supported the key aspects. Available in English and Spanish. Translators were available if needed. All participants then read the simplified document with an investigator and filled out the Assent Form Comprehension Questionnaire (6 V / F questions). A researcher clarified areas not understood. Finally they signed the document Follow-up period: Do not Toll: Ns	Mean age 15.12 years, with range [12-17]. Male 62.6%, Hispanic 69.9%. 56% correctly answered the 6 questions, and 22% correctly answered 5 questions. 26% mistakenly believe that they will be given the vaccine they will receive (Q4), 21% mistakenly believe they are guaranteed participation in future studies (Q3) and 15% believe they will receive free medical care through the study. Questions about randomization (Q2) and study withdrawal (Q6) were comprised of at least 89%. The variables of age, sex, race, weight, sexual identity, sexual history, smoking, alcohol, marijuana, place of residence do not significantly influence comprehension. Only participants from Baltimore, Maryland, obtained better scores (p = 0.0029)	An important step in ensuring full understanding of the study is the evaluation of understanding through a questionnaire. The understanding of the information with a modified document is similar in all ages analyzed. The total understanding, of all the sections of information, barely exceeds 50%. Concepts such as randomization and right to revoke, are the best understood. Educational feedback in aspects not understood improves the understanding of information. LIMITATION: The educational level is not analyzed	It evaluates the understanding of a modified document in text format with supporting images, CI for adolescents [12-17 years] with an ad hoc questionnaire with 6 V / F questions.	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Larcher, 2010	Design: Descriptive, Review of the literature Goals: - Consider the ethical and legal nature of the competence to receive medical treatment - Provide practical guidance on how and by whom it should be evaluated - To determine the circumstances in which the assistance of a specialist is necessary Period of realization: N / Not applicable	Number of participants / group: 3 groups: over 18 years old, under 16 - 18 years old and under 16 years old Participating Features: Only specify age groups.	Intervention: There is no intervention in this article	NATURE COMPETITION: depends on the ability to understand nature, purpose and consequences and ability to decide. Competition is task-specific, impact on the child's future. It must be free of physical and mental influences. The capacity for autonomy is a continuous variable, but the competition is dichotomous (yes / no). The level of competence required for certain tasks is unknown, depending on the risk involved. TEST TO MEASURE COMPETITION: There is no single test, but it implies: the possibility of choosing that implies the ability to understand; the reasonable outcome of the election by making a decision that is considered correct and responsible; choice based on rational reasons, compatible with a life plan; ability to understand the need for treatment and its reasons, risks, expected benefits and alternatives, including non-treatment. It must also be able to retain information long enough; understanding, and not potential, and evaluate it HOW TO DEVELOP COMPETITION: Competence can be improved by sharing information that increases understanding of current treatment, its alternatives and the potential consequences of all options. Emotional	Although required by law, there is no single test to evaluate competition. It is necessary to evaluate competencies within the dynamics of working with children and families. Relationships based on trust, mutual respect and exchange of information should be encouraged. By adopting this approach, the need to dichotomize competition may be reduced.	Competence is related to COGNITIVE CAPACITY and EXPERIENCE and can be improved with education, incentives ... The participation of a psychologist or other third party should be considered in cases that pose serious difficulties in assessing competence or conflicts in complex decisions. Potential evaluators should have the necessary practical skills and understanding of the child in their social and medical situation. Assessments should be appropriate developmental, explore systemic influences and consider the child's emotional state, cognitive development, and ability to balance risks and benefits. The involvement of a psychologist or other independent third party should be considered in cases that raise serious concerns about competition, or involve complex decisions or conflicts between parties. In rare cases the courts may be involved. Proposal of questions to be answered: *Necessary information questions to be answered?* *What is the illness/condition and what are its effects?* *What treatments/investigations are necessary and why?*	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
				maturation includes developing the ability to consider the consequences of actions both for and for others. The children's personal experiences and their responses to it can provide them with a greater understanding than children of comparable age who lack such experience. COMPETITION EVALUATION: Physicians have legal responsibility, but other members of the multidisciplinary team may be able to do so. The assessment of competence must be individualized to a given context, although the ability to understand and evaluate risks is essential. Get relevant information about the child and his / her illness in advance. Allow enough time to decide. Check the level of development of the child to adapt the information. Explore external influences and emotional state that may compromise the child's ability. Evaluate cognitive development and its ability to assess risks and benefits. WHEN INVOLVING A PSYCHOLOGIST: In some teams, it is usual for the psychologist to evaluate competence with all the factors described above. At other times, it only participates when there is a conflict of decisions.		*When does this need to be done?* *What does the treatment mean to me, and how will it affect my life?* *What happens if I do not have the treatment?* *What are the alternatives and their effects?* *What are the practical consequences for me and my family on school and friends?*	

REFERENCE	STUDY	POPULATION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Leibson, 2015	Design: Bibliographical review of the literature Goals: This review addresses the historical, ethical, and legal aspects of IC for pediatric drug research. Period of realization: Ns	Number of participants / group: Bibliographic review NON-SYSTEMATIC	- The authors (Lee, Ondrusek, Hein) suggest that in children between [9.4-11.2 years], IC can be justified if their competence is demonstrated. Under 9 years suggest that they are not competent. - Other authors suggest that there are no clear indications as to the age at which the child is able to nod. - Hein proposes the use of the MacArthur-CR to evaluate the capacity. - The essential components of IC in pediatric research are: freedom of choice, non-coercion with rewards, complete and understandable information (including drug, risks and potential benefits if any, procedures), in plain language - Information in writing - The amount of information must be decided for each protocol. Amount of reasonable information the patient wants to know - In a suitable format: multimedia, in group to favor interaction - Confidentiality. If this is not possible, please inform - Assent or agreement expressed by the minor and right to revoke at any time, of children who understand the purpose, risks and benefits. - The concept of "mature child" is not used in research as the interventions do not in many cases offer a direct benefit to the child. Instead in treatment yes.	The ethical peculiarity in pediatric research is what concerns the IC process. Changes in the lifestyle of adolescents necessitate the evolution in the consideration of the maturity of the children	It is a bibliographical review that addresses the evaluation of the CAPACITY of the child linked to age, understanding and reasoning. Provides guidelines on the essential components of IC in pediatric research	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Massimo, 2009	Design: Monocentric study, transversal and descriptive survey project Objectives: To evaluate the degree of awareness of sick youngsters between 11 and 18 years of age with regards to the experimental trial they are undergoingTo estimate the proportion of patients with an acceptable level of awareness period of realization: 18 months	Number of participants / group: The minimum number of patients to be interviewed in this type of study will be 120, acording to Machin and Campbell Participating features: No	Intervention: Semi- structured interview with 11 simple items. The form includes 2 sections: the first one is private and is reserved for the Hospital staff. It collects the patient´s personal information; and the second section includes 11 items for the patient´s awareness evaluation, which is given by a trained pediatrician. One single encounter which will last approximately one hour. It will take place no sooner than one month from the start of the protocol and no later than one year after. Follow-up period: 18 months Number of losses: N/Not applicable	It´s a project. There is not results	There are not conclusionsThe model suggested implicitly demands that proper and factual information must be given to children and adolescents via simple dialog with the interviewer. It is the autors wish that this interaction, for all practical purposes, will become a routine part of hospital life, and that it will lead to an improvement in the patients and families quality of life	It is a project. The purpose is interesting, but it need to be evaluated.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Miller, 2014	Design: Observational, descriptive and qualitative with recording of CI interviews. The ICC audio tapes were transcribed, anonymised, verified and loaded in NVivo 8 for encoding and analysis In addition, he included interviews with a group of 18 patients aged 14 - 21 a. Goals: -Describe the participation of children and adolescents by measuring physician-patient and parent-patient communication during the IC conference -Try if participation in IC discussions	Number of participants / group: n = 61 Participating Features: Age, sex, type of cancer, years since diagnosis, duration of communication, role of physician, EC phase I	Intervention: Consent conferences were recorded, transcribed and coded for communication between patient - physician and patient - parent. CI in writing, in children aged 18 - 21a. Verbal or written assent, in children from 7 - 17a. Patients aged 14 to 21 years were interviewed to evaluate additional variables related to the decision Follow-up period: June 2008 - June 2011 Toll: 3	- In the word count, it was observed that in 2 cases there was no doctor-patient communication, in 3 cases there was no parent-patient communication and in 10 cases there was no patient-parent communication. - The average proportion of communication from the doctor to the patient was 36%, from the father to the patient, from 1.76% and from the patient to the father it was 0.57% - 73.28% of the doctor's communication was to give information, 8.73% was to ask and verify, 7.34% socioemotional, 5.74% to establish the agreement and 4.8% was personal. Regarding the participation of the patient; was involved speaking in 43% of the communication, and gave	The majority of physician-patient communication consisted of providing information. The creation of a climate of trust and a social-emotional exchange, increases the satisfaction in the decision making. The difficulty to understand and the perceived pressure to participate were generally low in the subsample of patients aged 14-21 years. However, when physicians increase communication with their patients, they perceive that the information is easier to understand. It is possible that direct communication with patients is an indicator of other aspects of communication and may be related to the results of participation. The mean proportion of patient-to-physician communication was low. In 10% of cases, the patient was asked to sign the IC form without asking for an	Direct communication and creating a climate of trust between the physician and the child in the decision-making process of a Phase I clinical trial is very important in order to obtain a truly informed consent. It is not only important to give information, but also to talk about many other socio-emotional and personal aspects (emotional state, feelings, doubts, suggestions)	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	increased with the patient's age - Examine whether participation was associated with patients' perceptions of the difficulty of understanding the information, the pressure to participate in the Phase I trial, and the difficulty in making the decision. Period of realization: 06/2008 - 06/2011			an opinion in 67% of the cases. In 10% of the cases, an opinion was not asked for, but he was asked to sign the IC. Regarding the age; the physician's communication was positively associated with the patient in the range of 18-21a, but communication from patient to physician was similar at all ages. Regarding the interview with the group of 14-21 a (n = 18); when physician-patient communication increased, patients perceived the information to be easier to understand. In the patient-physician communication, the difficulty of understanding, the perceived pressure or the difficulty of decision making did not influence.	opinion about the trial or treatment.		

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Miller, 2013	Design: Analytical, observational study Goals: - To examine the perspectives of adolescent patients about understanding and making decisions about a pediatric phase I cancer study. Period of realization: Jun 2008 - Jun 2011	Number of participants / group: n = 20 Participating Features: Age [14-21a], Cancer, candidates for an EECC phase I, with sufficient cognitive capacity to be able to understand the information	Intervention: - Comprehensive interview focusing on four areas related to decision making on Phase I research: 1) understanding 2) the decision-making process, including the role of the adolescent, the impact of faith on decision and perceived pressure, 3) expectations regarding the effect of participation in the essay on the quality and duration of life 4) reasons to accept or reject the Phase I study. Participants answered closed questions about a verbally administered structured interview, which evaluated aspects of understanding and decision making about the Phase I study.	- 7 participants from [14-17a], and 13 participants from [18-21a]. - 75% were boys, mostly Caucasian (80%), with bone or soft tissue cancer (55%) followed by brain or CNS cancer (35%). - The mean number of years from diagnosis to participation in a phase I trial was 3 years on average. - UNDERSTANDING: After the IC lectures, 90% understood that it was not necessary to participate in the trial to be attended in the hospital, 90% understood that they could be withdrawn at any time and that the trial involved risks. 30% indicated that the trial would provide medical benefits, and 50% said "I do not know". -LEGIBILITY: The information provided was considered easy to understand (mean = 1.95 on a scale of [0 / very easy - 10 / very confusing]) - DECISIONS: 85% had the final word on the final decision to participate, considering that they are the most influential people on the decision (50%) and their parents (35%). Participants rated the opportunity to ask questions to the "high" doctor (M = 8.95 on a scale of [0 / not much-10 / lot].) Faith was important to the decision in 50%. (M = 2 on a scale [0 / without pressure - 10 / a lot of pressure].) The expected effect of their participation was investigated with questions 50% expected an improvement in their quality of life, and 80% expected them to last longer. The reasons that led them to participate were 75% of the cases, a	Section of conclusions very general. He speaks that the knowledge gained will help guide physicians and researchers to improve the IC process in Phase I and can be applied more widely to other potentially vulnerable subjects.	The investigation is limited to [14-21a], children with cancer participating in a phase I trial. Understanding the information is quite good, although under the benefits section there is a big misconception in the adolescents' belief of a benefit direct improvement in their quality of life and life span. The decision-making process seems easy enough, and most do not feel pressured	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			Follow-up period: jun 2008 - jun 2011 Toll: Ns	potential positive clinical effect, including cure or 45% said because there was no other treatment option, 20% said to contribute to science or to help others.			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Monaghan, 2009	Design: Descriptive, transverse. Goals: - Establish a more robust approach to obtaining the consent of 12- and 14-year-olds participating in surveys based on existing practice of "negative consent" and completing it with competent Gillick Period of realization: 2002-03 and 2004-05	Number of participants / group: Group 14 years (2002-03), n = 6393. Group 12 years (2004-05), n = 6749 Participating Features: By age, yes. There are no more sociodemographic variables analyzed.	Intervention: 1st CI is requested to the parents by postal mail. 2º an intervention is made explaining to the children who are going to participate on the nature and purpose of the exploration. Doubts are resolved. 3º is carried out the exploration. 4th is an interview with 4 questions about his experience. Three questions with an answer YES / NO about understanding what the dentist would do, why he would explore his teeth and if he was treated well, and a fourth with an open answer about why he thinks he was not treated well. Follow-up period: 2002-03 and 2004-05 Toll: 5 losses in the group of 14 years, and 17 losses in the group of 12 years	-The 10% of 12 years and 9% of 14 years, did not understand what the dentist would do (nature of the scan). -The 13.8% of 12 years, and 11.7% of 14a, did not understand the reason of the exploration (purpose of the exploration). -The 99.9% of both ages were satisfied with the way they had been treated. Those who were not satisfied indicated the reasons. - From the bivariate analysis, it is observed in children of 12a that only 83% understand the nature and the objective, and in the group of 14 a, 86%	- The use of the "competent Gillick" concept in Wales did not affect participation rates negatively. - There is still uncertainty about how dentists should assess the competence of children - Legislation presumes non-competition, and lets the dentist judge the competition - If only children who understood the nature and purpose of what was proposed were included, 15% could not have participated despite the opportunity to ask questions - The exchange of information, the explanation, the opportunity to ask questions as a basis for assessing the capacity	In Wales and England non-competent children are considered. An adult is considered competent in England and Wales if he is able to understand relevant information, withhold such information, weigh up such information to make the decision and communicate the decision. The law recognizes that the level of competence necessary to make a decision without risk is lower than that required in a more complex situation with different alternatives. It does not refer to research.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: O´Lonergan, 2011	Design: A first descriptive study (survey) and a second analytical, experimental, randomized trial of understanding between traditional paper format, and the new multimedia format for two hypothetical research studies on dualenergy radiograph absorptiometry (DXA) and abdominal ultrasound. The general hypothesis was that children and their parents exposed to a multimedia permission / assent (P / A) process would have better understanding compared to those exposed to a traditional paper-based process. Goals: - Develop audiovisual descriptions of procedures and research rights for incorporation into a	Number of participants / group: A total of 194 pairs of child-parents (children 11 to 14 years): 24 pairs of child-parents in a pre-study on components of preference by survey and the effect on comprehension and 170 pairs of children-parents (340 participants) in a randomized trial in multimedia or paper for the assent in a hypothetical study Participating Features: Group surveys: age, marital status, employment, educational level, race, ethnicity and any medical diagnosis of the child.	Intervention: GROUP SURVEYS: 9 questions on the preference of the format (video, text, animated) and 10 comprehension questions (5 for each DXA / ultrasound procedure) on risks were analyzed, if the child has to wear hospital pajamas, how is the procedure and the part of the body to explore. RANDOMIZED CONTROLLED TRIAL GROUP: with the results of the first group, documents were designed in text and multimedia format with explanatory hyperlinks (3 hyperlinks on assent, which is an essay and right to revoke and 2 others with videos about the procedure and risks), for the hypothetical participation in a research study. The text with short sentences and appropriate to the age. We then analyzed the cognitive function of children with 2-subset Wechsler Abbreviated Scale of Intelligence and the parents a demographic questionnaire.	SURVEYING GROUP: Most of the study subjects prefer the video version of the DXA on the animated version and the paper (41 of 48 [85%]; P <.0001), and there were similar results for the description of abdominal ultrasound 38 of 47 [81%], P <0.0001). There was no difference in the comprehension of children with the 3 versions, but the group of parental media had significantly improved overall comprehension (P <.03) compared to paper format. RANDOMIZED TESTING GROUP: children were within the range of normal intelligence for their age. Children exposed to the new multimedia format showed a better overall comprehension compared to the paper format (P <.0009), and	Multimedia approaches to the decision-making process or assent can improve the general understanding of research involvement for children and parents. Better understanding of the specific components of the study can improve general understanding.	This article considers children> 7 years old, able to lend their assent. The hypothetical research study involves low-risk procedures, and the risks were not well understood. The use of a multimedia format (video, computer with explanatory hyperlinks in voice-over) improves the general understanding of information in children and parents in the process of assent.	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	process of assent and then determine if the incorporation of these media improved the understanding of parents and children. - Compare the understanding between a multimedia permission / assent and a traditional process with text. Period of realization: Ns		With EVA [0 / I did not understand anything - 10 / I understood everything] analyzed how much they understood. In addition, questions were asked about the 8 essential elements of the consent process (objective, procedure, risk, direct benefit, indirect benefit, alternatives), and post-consent comprehension interview (PPCI) , right to revoke, voluntariness] that were recorded, transcribed and codified [0 / non-comprehension, 5 / correct but incomplete, 10 / correct and complete] Follow-up period: Do not Toll: Ns	there were very significant differences in the understanding of study procedures (P <.0002) and risks (P <.0001). The risks were not very well understood by the children, nor by the parents, but in all was better the score with the multimedia format. All children and parents overestimated their understanding.			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Poston, 2016	Design: Descriptive, longitudinal of mixed methods. A QUANTITATIVE approach with the use of the Quality of Informed Consent Questionnaire (QuIC) with an adolescent population and their parents / guardians, and a QUALITATIVE approach with qualitative semistructured interviews with adolescents, their parents and physicians in the 48-72 hours of IC and consent for a clinical trial of pediatric oncology, and retention analysis of information 6-9 weeks after the initial IC. Goals: -Describe informed consent and consent experience in cancer research from the perspective of the participants: adolescents, their parents and their	Number of participants / group: 4 adolescents, 4 parents and 3 physicians Participating Features: ADOLESCENTS: 3 boys and 1 girl, African American, 12-18 years old, with myeloid leukemia (1), hodking lymphoma (1) and sarcoma (2). No previous research experience. Included in a phase III clinical trial of oncology. PARENTS: 4 African American women, 35-54 years old. Only one of them had previous experience with a research study. DOCTORS: 2 men	Intervention: 1º Adolescents and their parents or guardians will participate in separate programs or qualitative interviews recorded in audio that last approximately one hour. Adolescents and their parents / guardians were asked to provide a description of their IC process and their subjective experiences. Seven key issues were analyzed; altruism, pressure, fear and lack of control, communication with the investigator, time and haste, protocol and memory. 2 The subjects completed demographic data and the questionnaire (QuIC). The researcher completed the diagnosis of adolescent participants. 8 domains relevant to ICQ quality measurement with QuIC: Part A measures objective comprehension [1 / disagreement, 2 / unsafe, 3 / agree] and part B	QUANTITATIVE ANALYSIS COMPREHENSION (QUIC): in a scale of 0 to 100, where 100 is the maximum comprehension, TEENS obtained in part A (objective comprehension) obtained scores between 53 - 72, with a mean of 64.25. In part B (subjective comprehension) the scores were higher, between 60 - 89 with an average value of 79.25. In both parts, the scores were better in the female sex. The PARENTS obtained in the part A, lower scores between 47 - 70 with an average of 59, and in the part B higher between 86 - 100, with an average value of 93.This indicates a low level of objective comprehension of the essential elements of IC and assent, and a high subjective level of understanding. QUALITATIVE ANALYSIS (INTERVIEWS): ALTRUISMO, parents and children want to participate well by helping others, or by family pride and physicians to collect data for	QuIC could be used shortly after the discussion of IC and AI followed by qualitative interviews to explore the origin of participants' misunderstandings. The positive impression of the relationship with the researchers facilitated the experience of consent and assent. The participation of adolescents demonstrated the need to use a language they can understand, a high level of interaction and their involvement in the decision-making process. Researchers should know the adolescent and his / her particular situation well, and identify specific informational needs of each of them and their families	Little sample. Good method. Use of QuIC interesting. The qualitative interview shows many data that can not be collected through a standardized questionnaire.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	medical providers. - Determining the understanding of key elements, memory and memory in detail time. Period of realization: Ns	and 1 woman, Caucasian, between 35-44 years old. They were the principal investigators of the trial and had prior experience in pediatric research and training in ethics and consent / assent in research.	measures subjective understanding [1 / do not understand at all 5 / I understand it very well] with final score of 0 - 100. Estimated time 7 minutes. 3º A second qualitative interview with adolescents and their parents / guardians 6-9s after the end of the Induction Phase for the clinical trial on cancer Follow-up period: Do not Toll: Ns	the future. PRESSURE, adolescents and mothers felt overwhelmed with the vast amount of information and complex concepts. They emphasize complex language, very sophisticated. FEAR AND LACK OF CONTROL, adolescents and parents express fears and lack of capacity to manage oncological diagnosis, treatment options and decisions. Mothers express clear feelings of panic and lack of control, which they disguise in front of their children to protect them. COMMUNICATION WITH THE PHYSICIAN, is considered positive by adolescents and mothers. They used positive communication techniques and made them feel part of the conversation, emphasizing a patient-centered approach. Physicians noted their strategy of using plain language and physical signs that reflected differences in power between doctor, parent, adolescent, and nurse were eliminated.			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
				TIME / PRESS, expressed frustration with the accelerated pace of decision making and pressure. They do not have time to process the information. MAP OF ROUTE, was explained by parents and adolescents with the order of activities and time schedule. This route map came from the doctor explaining the scheme of the protocol. MEMORY; mothers and adolescents described an inability to remember specific IC content and assent. The feeling of being overwhelmed and flooded with so much medical information was pointed out as the cause. ANALYSIS INTERVIEWS 6-9 WEEKS AFTER: Parents and teens struggled to remember details, but their feelings of fear had waned as they saw progress and reached milestones in protocol. They attributed this to their trust with the doctor			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Raymundo, 2008	Design: Descriptive, cross-sectional study to evaluate moral development using the LOEVINGER MODEL OF EGO STAGES Goals: - To evaluate the moral development of a group of minors and a group of elders, using the classification system of moral development proposed by Loevinger as an indicator of the capacity of consent. Period of realization: Ns	Number of participants / group: 59 adolescents aged 14-18 years, and 60 patients aged> 60 years Participating Features: Partially	Intervention: Two psychologists, trained and prepared to use the instrument, identified possible participants in the waiting rooms of the consultations described, approached the patients, asked permission to speak with them and explained the research study related to the moral development of individuals and that it was anonymous. If they agreed to participate, they had to answer a 10-minute questionnaire, marking personal preferences. We used the Souza questionnaire validated in previous studies, and codified with the author's proposal. The instrument includes 30 states, distributed according to the Loevinger model with 9 possible answers each. Follow-up period: Ns Toll: Ns	SOCIODEMOGRAPHICS: the group of adolescents (n = 59) had a mean age of 16.08a, and 78% were students of low socioeconomic status. The mean age of the elderly group (n = 60) was 67.48a, mainly retired. YO DEVELOPMENT: adolescents, 15.3% conformist, 67.8% stage of consciousness and 16.9% autonomous stage. Of the elderly, 18.3% conformist, 61.7% stage of consciousness and 20% autonomous stage. No significant differences were found between the two age groups.	The ability to understand and decide, is gradually acquired, not suddenly when a child reaches legal capacity. Probably this capacity is acquired before legal. The moral capacity is individual and varies with the person. Age should be a relevant requirement, but it should not be the main determinant in the consent process.	The socioeconomic level of the participants was low, which may influence the level of moral development. It should be studied at other levels. It is also unknown whether sex or number of years influence. The ability to understand and decide does not depend exclusively on the age of the patient. Therefore, age alone is probably not a suitable variable to measure health decision making.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
Short quotation: Roth-Cline, 2013	Design: Literature review of the evidence regarding the IC of the parents and the assent of the children. Goals: -Review the evidence about the parents' IC and the children's assent, including INFORMATION, UNDERSTANDING and VOLUNTARIETY. -To highlight the differences between the child and the adolescent about the assent. -Consider the circumstances in which the parents' IC can be waived or the children's assent Period of realization: Ns	Number of participants / group: Evidence review. It does not indicate revised articles or search criteria. Participating Features: The review is made of two population groups: parents, children and adolescents.	PARENTAL PERMISSION: information on potential risks, benefits and alternatives. Willfulness. The permission of one of the parents is sufficient, as long as there is a minimal risk and with direct benefit to the child. Failure to do so requires the permission of both parents. A parent's perception of understanding at the time of decision may be high, although the parent may be unable to remember concepts in time. The criteria that improve the understanding of the key concepts are: that they can think clearly without being overwhelmed by emotion, education level, clarity in the disclosure of information, having a child in a previous study, age of the father, how they read the document of CI, the time they have to decide, amount of information. On the other hand, education, gender, social minority, lack of previous experience and lack of information are significantly associated with voluntariness. It also speaks of "continuous permission" throughout the different stages of the trial, to improve quality and the use of multimedia presentations to improve the perception and understanding of relevant information. CHILD ASSENT: The regulations specify factors to be taken into account to assess ability (age, maturity and psychological state). The regulations do not specify the elements of information necessary for the child, but according to the recommendations of the National Commission, the consent must include information on: procedures to be carried out, freedom to choose, communicate decision and possibility to withdraw. In order to obtain	The principle of respect for people requires that both the father and the child, if able, voluntarily choose to participate in the research. Parents should be provided with detailed information about the nature, objectives, risks, benefits and alternatives. Children who are capable, must agree to participate. The amount of information a child should understand must vary with the child's age and maturity. The age at which a child is able to assent may be less (5-7a) if it is understood as an expression of willingness to participate. The assumption evolves from a choice of young children depending to a large extent on the decision of parents, to joint decision making as the children mature, to a widely independent decision taken by an older adolescent with parental affirmation. More research on volunteerism is needed. We do not know the predictors of voluntariness nor the influence of family and medical	Parent IC and child assent contain components of information exchange, understanding, and willingness. How these three components are understood and operationalized should differ depending on the development level of the child The only empirical instrument to measure voluntariness is Decision-Making Control Instrument (DMCI). The instrument for measuring capacity, MacCAT-CR	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
			the agreement according to William Bartholome there are 4 essential elements: development of the appropriate understanding, revelation of the nature and procedures, evaluation of the influences that the child can have and their understanding of the information, and the will of the child. A more standard measurement to determine children's understanding is the MacCAT-CR: its use is feasible, acceptable time and excellent reliability in children. But there is no competition threshold (it should be in line with the relevance of the research and its risks) and its use has not been validated in a larger pediatric population. Evidence available suggests that the ability to understand medical decisions among adolescents older than 13 years is similar to that of adults.	equipment		

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
Short quotation: Scherer, 2007	Design: Non-systematic bibliographic review Goals: -Review the literature related to knowledge, competence, will and economic compensation in the decision-making process in biomedical research with children, adolescents and their parents. Provide clinicians and researchers with an analysis of key issues related to voluntary consent for research and assent of the child. Period of realization: Ns	Number of participants / group: Bibliographic review. It also does not apply to the selection of articles. Participating Features: Ns	KNOWLEDGE: The majority of studies focus on researcher-patient communication. Regarding the empirical studies that exist, they say that written IC forms are tedious and difficult to read and understand by people who lack medical knowledge. Poor communication between adolescent and physician may occur when risks are described. In the case of children, most of the information on diagnosis and treatment is addressed to the parents, who filter and modulate it. Adolescents can attend more and may feel more responsibility for decision making when the study is presented directly to them and their parents will ask more questions when their child is not present. Parents and teens may be better informed with separate discussions. COMPETENCE: From a psychological perspective, there are several variables that can be used to judge an individual's cognitive abilities and the maturity of decision-making. An important consideration in the differential perception of risk between adolescents and adults may be the distinction between risk and aversion. Adolescents may need adult support when faced with participation in medical treatment decisions. The ratings of benefit parents and teens are fairly similar, although parents tend to be more hopeful in their BENEFIT perceptions, whereas parents and doctors are less concerned about the risk and aversion of venipuncture than adolescents. Both physicians and adolescents seem less concerned about the risks associated with	As pediatric asthma researchers recruit and enroll adolescents and parents in studies, they should be sensitive to the interpersonal process of establishing trust and credibility with both parents and adolescents. These interpersonal processes are not static and during the duration of the study More than a single conversation and consent signing event, discussions about research procedures, risks and benefits should occur on a regular basis throughout the duration of the studies among adolescents, participants and their parents. There are differences in understanding between adolescents and their parents about the appreciation of research risks and procedures, and compensation can be an influential factor in the decision-making process	Little-structured bibliographical review. It analyzes 4 key sections, but without giving any conclusive data. Each section ends by counting what they have obtained in asthma research, but without significant data. It seems more like a set of opinions.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
			experimental medication than parents. VOLUNTEERING: Many IRBs support the review of federal regulations to allow adolescents to independently consent to some types of research, including anonymous surveys, biomedical studies that only venous puncture, minor risk investigation at minor maturity, and drug-approved the FDA for pediatric patients. The Society for Adolescent Medicine (SAM) supports this position and has developed guidelines that articulate analyzes and recommendations of situations in which adolescents can ethically provide informed consent for participation in research. The degree of autonomy granted to adolescents varies culture, gender and age of adolescents. In general, young adolescents tend to differ or submit to parental authority, in mid-adolescence they begin to affirm, and try to exercise, greater control over personal choice. Adolescents are given more autonomy at a younger age than girls ECONOMIC COMPENSATION: Studies that require more time, effort, and discomfort usually offer greater compensation than they anticipate as "fair." Whenever financial compensation exceeds expectations, it is unethical. Avoid "overcompensation"			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
Short quotation: Scherer, 2013	Design: Review of a subsection of the empirical literature on adolescent consent Goals: - To determine the competence to assent to adolescents participating in clinical research on asthma and cancer - Assess the risk perceptions and benefits included in the protocols - Establish the effect of social and contextual variables on decision making - Relate it to psychological and social factors. Period of realization: Ns	Number of participants / group: Bibliographic review that does not specify the number of articles reviewed	It is a complex way in which research, protocol characteristics and family dynamics mediate the process of assent that adolescents and their parents participate when they approach participating in pediatric asthma research Studies on understanding risks and benefits suggest that adolescents and adults often perceive benefit from research where it does not exist. A positive relationship with a physician-researcher may improve research protocols for adolescents and parents, but medical researchers should also be aware about alerting parents and especially teens about the risks of participating in research, clarifying the differences between the discomfort and the risk of procedures, and articulate clearly the prospects of personal benefit	Given the variability in adolescent maturity, diversity of family decision-making styles and the logistics of seeking adolescent consent and parental permission, researchers should use flexibility in designing a process of assent. In cases of mature adolescents who make minimal decisions about participation in research, it is entirely reasonable to seek the assent of adolescents outside the presence of their parents. With less mature adolescents and more risky research, family-level adolescents consent / parent permission conferences may be more The degree of financial compensation influences decisions to participate in research. This may be lower in studies of minimal risk. However, over and above the minimum risk studies that offer substantial compensation for participation in research requires a careful presentation of how the appropriate compensation will be distributed. At family conferences, researchers could increase teen participation by assuring parents, especially authoritative parents, that teens' views are vital to the research effort and teens to voice their questions, concerns and preferences.	Variability in the maturity of adolescents (diagnosis, previous experiences, cognitive area, neurological development, social-emotional area) and it is difficult to generalize a consent process. What seems clear, is that AGE can not be set as standard. It is also common, the difference in the perception of risk and benefit. If the perception is positive, and accompanied by financial compensation, the probabilities of assent are high. Family dynamics are also key in the decision-making process	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Swartling, 2011	Design: Qualitative study through free narrative interviews in focus groups. Interviews were conducted with the children participating in the ABIS study on DM1. It is a longitudinal study in which they entered at birth. Interviews are done with the cohort who was 10-12 years old at the time of data collection. Goals: -Explor the views of children under 10-12 years of age on medical research and participation in such research. Period of realization: Period of 8 months, between 2009-2010	Number of participants / group: n = 39 children. 6 focus groups (1 group with 5 others with 6-7 children); 3 with no experience and selected at random by the teacher and 3 with experience in ABIS Participating Features: 3 groups without experience and 3 with previous experience in ABIS. 20 women and 19 men.	Intervention: The interviews were digitally recorded and transcribed digitally, with each participant assigned a pseudonym. Field notes were also taken during interviews Each child was asked to: (1) Medical research (What is it and what do researchers do?) (2) Children and research (Why do children participate in research?) (3) Information and consent / consent / dissent (What do children want to know and decide if they are participating in the research?) (4) Data collection (What samples do researchers take and what do they do with them?) (5) Consequences of research (What do researchers find when children are involved in medical research?) (6) Risk of disease (What is risk taking and would you like to know?) Each topic was introduced by asking: "Can you think and tell me about ...? " The interviews were analyzed in three stages. In the first	5 topics: (1) knowledge about research and its importance. All groups considered IMPORTANT research and a positive image of researchers (2) a sense of altruism. There was a clear idea that the research was to "help" people (not just children) and everyone, regardless of their experience, believes it is important to share the data with others. Most stressed the importance of being informed of the final results. There was a homogeneous feeling that "A reward" could in some cases be good, but not in the "real" investigation, since it was then "bribe" (3) shared decision-making and the right to dissent; Age is important, and 10 years is an "appropriate" age in which they could understand information about the research and be able to participate in discussions even though they mention age 5-7 to start informing children about research. Most favored shared decision-making (family	Children are positive for research and when they participate, they want to be actively involved, take part in decision-making, and have their integrity and interests respected and protected. The process of informing children and making sure they understand what they are involved in is vitally important. This problem is even more important in prospective research. Appropriate information may be important to promote willingness to continue to participate in such studies.	Medical research on children is vital (1) ensure understanding of children's participation, (2) foster shared decision-making and (3) report on the final results. Information on research participation and outcomes should be appropriate for the age and maturity of the children. The five themes that emerged in focus group discussions are good starting points for discussions about children's participation in medical research: (1) knowledge about research (2) a sense of altruism, (3) shared decision-making and	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			step, we have made an account of each child's experiences and thoughts. In the second step, individual stories and interviews were analyzed in terms of "themes". both steps also use field notes. In the final step, two of us brought together the common themes of the groups approach, showing shared experiences. Follow-up period: Interviews were conducted for 8 months, between late 2009 and early 2010 Toll: N / Not Applicable	decision) rather than individual consent. Many children preferred written information individually rather than using information technologies such as e-mail or websites (4) notions of integrity, privacy and access: all children were very positive in allowing other researchers to use their data in other research projects. Do not think they can be used for anything bad (5) Understanding the risk of illness and responsibility: All groups held that it was good to be informed about things that could make children sick, because then you could do something about it		the right to dissent (4) notions of integrity, privacy and access (5) understanding of disease risk and personal responsibilities.	

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Twycross, 2008	Design: Qualitative study of working meetings held during the Research Society's international nursing research conference. Goals: -Provide good clinical practice in finding an informed agreement for children involved in research. -To know if it is possible to obtain IC from small children -Determining the researcher's commitment to the child -Know strategies for finding informed agreement for children to participate in	Number of participants / group: The number of workshops, or documents analyzed, is not known Participating Features: Ns	Intervention: Working meetings were held between members of the Royal College of Nursing's Research in Child Health and the UK Association of Child Health Nurse Researchers to discuss age-related issues to agree on research and strategies to be used by the investigators. Follow-up period: May 2007	- Children of ages 2 and above could claim to participate, with process adapted to them - Suggestions to establish relationship: Begin by explaining to the child who you are and how you are connected to your environment. Provide opportunities to meet the child (if they do not already know) and to get to know you. This makes it easy for the child to ask questions. Sit down and make eye contact with the child. Request permission to turn off the TV and minimize other interruptions and distractions where possible. Start by asking the child if he or she has been told something about the study. Be patient and demonstrate that you are prepared to wait for the child to think and speak, instead of thinking for him or her and jumping in too early. Always ask the child to clarify what he or she is trying to express rather than guessing what he or she means. Think about the types of questions that should be asked to be sure that the child has	-The values of respect, trust, clear information and good communication should exist when requesting consent in any type of project, regardless of the child's age - It is possible to obtain an informed consent to participate in a research study of children aged 18 months, provided that appropriate and attractive methods are used. - With young children, it is always necessary to obtain permission from the parent / guardian before approaching the child. - This is not a single procedure, but an ongoing process requires the researcher to commit to the child, using supportive materials such as information leaflets that have been prepared specifically for the minor child	It's a review article. The review methodology is not described, so the conclusions are not well supported. It picks up results from some random articles I imagine. Make suggestions without evidence.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	research -Establish a formula for information to be adequate Period of realization: May 2007			understood the research. (Open-ended questions are not always best suited to young children, as they may try to find the answer the adult is seeking.) Achieve a level of confidence in this first stage of a potential research relationship with a crucial child and is based on that researcher son who is really interested in what he or she has to say. - Strategies for assent: getting a good understanding of what will happen, what you want to achieve and the ability to decide to participate or not. To ensure that they understand it they propose several forms: one is asking questions at the end of the information, another is a table of activities as a game for the little ones, and in a fun way, another strategies is to let the child talk to others about the participation. - Formatting suggestions: The information should be kept to a manageable length, according to age and development. The sheet should not have more than one double-sided A4 page (detailed information sheets can overwhelm the participants). Brochures should be designed so that they can be read to the child but interactive			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
				enough to be involved in the process. The language used should be appropriate for the child's age and stage development. Images can be used to increase commitment, but appropriate for child development, prior learning and setting. Do not just increase the size of the typeface of an informational brochure originally designed for older children. Information leaflets should be printed on the letterhead of the hospital / institution where the research is conducted. Normal paper is not acceptable even for young children. Information leaflets must include the information required for consent, as established by NRES. This can mean being creative in the way you formulate the question or provide information or the child may not fully understand. If images or graphics are included, they should be simple, clear and familiar. Always respect the confidentiality of the data. If this is not the case, the child should be informed.			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Tait, 2017-a	Design: Based on current guidelines, a preliminary definition of ASENTIMIENTO was generated and Delphi Panel was sent, which included experts in bioethics and pediatric researchers, members of the Institutional Review Board, parents and individuals with regulatory / legal experience. For each subsequent review, the process of summarizing and reviewing responses was repeated until a consensus was reached. Goals: -Develop an	Number of participants / group: 20 participants in the Delphi panel: 11 pediatric research experts, 7 institutional review teams, 9 bioethics experts and 3 law experts Participating Features: 11 men and 9 women. All of them parents	Intervention: A PRELIMINARY DEFINITION is established: "An interactive process between a researcher and a participating child that involves an appropriate development, disclosure, discussion and understanding in which the child freely asserts his / her agreement to participate in a proposed research study but has a maturity or lack in the absence of an affirmative agreement, the mere failure of the child should not be construed as consent. " With this preliminary definition, 4 rounds were made with experts until reaching the final definition. The same was done with four constructs: the child's assent, information for young children (7-11a), information for older children / adolescents (12-17a), and requirements for meaningful consent	FINAL DEFINITION: "*Children who lack the legal authority to provide informed consent per state laws should provide their assent to participate in a research study unless they either lack the cognitive ability, their clinical condition precludes their ability to communicate a choice, or the research holds out the prospect of direct benefit that is only available in the context of the research. Assent is an interactive process between a researcher and child participant involving disclosure of cognitively and emotionally appropriate information regarding, at minimum, why the child is being asked to participate, a description of the procedures and how the child might experience them, and an understanding that participation in the study is voluntary. Children should understand that they can decline participation or withdraw from the study at any time. Assent requires that the child explicitly affirms his or her agreement to participate in a manner that reflects their age-appropriate understanding and that is free of undue influence or coercion. In the absence of an explicit agreement, mere failure of the child to object cannot be construed as assent.*"	The central consideration of assent as "Affirmative Agreement" was retained, but in each round of context revisions the importance of assent was added as an "interactive" process. It provided elements of information that were considered most important but also reinforced the importance of age-appropriate information that takes into account the cognitive and emotional aspects of the child.	The final definition is very dense, but it covers many important aspects. Regarding the information to be contained, there seems to be a consensus that you will be informed of: the procedures to be performed and how the child may experience them, the purpose of the study, that there may be no expectation of personal benefit but that their participation can help other children, that the study is voluntary, and that they can withdraw at any time.	Medium

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	operational definition of assent to ensure that investigators, review boards and legislators consider the process of assent in the same way Period of realization: September 2015 - May 2016		Follow-up period: September 2015 - May 2016 Toll: 13 losses; 8 did not respond and 5 responded that they did not	Consensus was also sought in 4 constructs, and the final results were: 1 Assessment of the child's ability: it can typically be done with a discussion with the child alone or together with the parents to measure maturity and cognitive ability. Health status and previous experiences in decision-making should be considered. 2 Information for young children (7 - 11 a) procedure to be performed and how it will be experienced, the objective of the study, indirect benefit if there is no expectation of personal benefit, voluntariness and right to withdraw at any time. 3- Information for older children / adolescents (12 - 17a), the same information but in some cases will do so without the presence of parents. 4- Requirements for meaningful assent: You must understand the basic information and be aware of how it would affect your situation. They must be free to decide without coercion or influence			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Tait, 2017-b	Design: The child-parent dyads completed separate and independent surveys of the information (risks, benefits, etc.) they perceived as most important for the child to make decisions about participating in a hypothetical randomized controlled trial. Parents responded in the context of what information they believed their child (not themselves) thinks important Goals: -Compare research information priorities of children and	Number of participants / group: 55 father-child pairs. N = 110 participants Participating Features: The mean age of children / adolescents was 12.8 ± 2.7 years. and 46.2% were girls. The majority were mothers (78.4%). Demographics by race / ethnicity of parents were: White 84.3%, African American 7.8%, Asian 2.0%, and Hispanic 5.9%. The majority (83.9%) of parents education beyond grade and high school	Intervention: Two questionnaires containing identical information were developed; one for parents and one for children. The questionnaire for parents was written at approximately the 8th grade reading level and the questionnaire for grades 4 through 5 with an age-appropriate formulation, according to Flesch-Kincaid reading level. After consent / consent, parents and children were asked to imagine that the child was being recruited for a randomized controlled trial comparing a standard versus new investigational drug for intractable headache. This hypothetical trial required the child to provide several blood samples for the pharmacokinetic analysis and complete a diary related to their experience of pain. Participating children and parents read the research scenario and then answered several questions about the relative importance of knowing the details of the study, such as risks, purpose,	55 dyads of parents and children completed the surveys (n = 110). Cronbach alphas supported the internal consistency of the survey items for both the child (? = 0.75) and the father (alpha = 0.80). The intra-subject correlation coefficients between the items of the survey of children and parents were 0.75 (95% CI: 0.64-0.84, P Children and parents classified all items as significant (> 7 of 10) Although children put more emphasis on knowing that their personal information would be confidential and less on knowing the purpose of the study and the benefits compared to what the parents thought their child would perceive as important. Adolescents give more importance in knowing what they would do to them, the direct benefits and nature of the study compared to younger children. There was no difference between the information priorities of the boys and girls. For parents, informational priorities were higher if their child was older (13-17 years old) and / or a girl. There was no difference in the parents' perception of their child's informational priorities for race / ethnicity. Parents with higher education believed that their children	The results show that the information priorities of children and adolescents participating in an ECA differs from what their parents believe is important to them. Pediatric researchers can use this knowledge to ensure that parents do not confuse expectations / priorities with their child's and that children receive the information they need.	Of interest was that while parents seemed to focus more on the importance of real risks, children seemed more interested in the burden of participation, ie how long the study might take and whether it would keep them away from their usual activities and in the confidentiality of your data. When it comes to making the decision, about 60% of the children want it to be shared. While it is true, a small percentage would like to make the decision themselves	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
	adolescents with information that parents believe is more important to their children -Determining who would want to make the decision to participate; the child alone, the parent alone or both Period of realization: Ns		benefits, etc. the questions were selected based on the literature on disclosure elements typically considered important by both parents and children. The importance of each piece of information (ie, risk, procedure, etc.) was rated from 0 to 10, where 0 = "I would not want to know (not important and 10 =" I really want to know "(extremely important). (ie, the child, parents, or both). Demographic information including age and gender of the child, race / ethnicity of the family, parent who completes the survey (mom / dad) and the highest level of parent training was also collected. A trained research assistant was present for parent and child surveys conducted separately and independently of each other and for younger children with any of the questions. Follow-up period: Do not Toll: Ns	would place greater emphasis on the importance of knowing procedures compared to parents with only one elementary or secondary school. Mothers with lower schooling believed that their children would put more emphasis on how long their child would be in the study compared to the more educated mothers. When asked who thought they would want to make the decision to participate in the headache study, both children and parents responded similarly. 64.2% of the children and 69.8% of the parents reported that they would want the decision to be shared. 11% of the children believed that their parents had to make the decision for them, while 5.7% of the parents thought that their children would want them (the parents) to make the decision for them. 34.5% of older children reported that they wanted to make the decision themselves compared to only 13% of the youngest children (P = .079). 10% of adolescents and 13% of the youngest children reported that they would like the father to make the decision for them			

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Unguru, 2010	Design: Recorded face-to-face interviews using the Consent Quality instrument (QuAs) Goals: -Determining what children (7-18a) with cancer involved in a clinical trial - Determine your preferences for inclusion in decision making Period of realization: January 2005 - September 2007	Number of participants / group: n = 37 children aged 7 - 19 a. 32 outpatient and 5 hospitalized children Participating Features: 37 children aged 7 to 19 years (mean: 13.6 years), 21 girls and 16 children. 70% immersed in a Phase III trial and 16% in Phase II. 38% take 12-24 months from the start of the protocol and 30% less than 4 months. During data collection, 38% had completed treatment and 62% were still in full treatment. All with a diagnosis of cancer.	Intervention: The 69-item QuAs instrument (open and closed questions) reviewed by 30 pediatric oncohematology patients familiar with the methodology of the research and child development trial. He was then evaluated by a scientist with experience in both bioethics and survey development. The instrument was pre-tested in a convenience sample of 4 patients with cancer and 4 between 7 and 16 years. Open-ended questions were included to facilitate a more nuanced understanding of children's views. The interviews were private, face-to-face, and audiorecorded, and lasted approx. 30 minutes. The children had the written questionnaire in hand and the researcher was reading aloud. Five dimensions of comprehension were evaluated: familiarity, knowledge (0-10), awareness (0-7), comprehension (6 intervention questions, randomization, risk / benefit,	FAMILY: 19% of the 37 children (51%) did not know or remember that their treatment was an investigation, although the terms "study" (95%), "research" (87%), "consent" , protocol (65%) ... 24% could not indicate which term best fit the type of research in which they were participating. KNOWLEDGE: in a range of [0-10], the mean was 5.7. 70% recognize that before participating, their doctor explained the ways they can treat their disease CONSCIENCE: in a range of [2-7], the mean was 4.8. Only 3 children could differentiate well between clinical treatment and research treatment. 41% do not know the purpose of the research in which they are participating. Only 5 children were able to correctly define the target. UNDERSTANDING: 70% said that information is "a bit difficult" or "very difficult" to understand, on a scale [1-3]. A minority replied that it was "easy to understand". 86% said they did not understand the language their doctor used. APPRECIATION: 89% say it is to generate knowledge, but 73% answered incorrectly about the risks.	Most children have a limited understanding of the research despite the doctors' explanations. Many children reported feeling they participate minimally in the decision to enroll in clinical trials. Tools to help researchers know that children understand what they agree upon when they agree to research and determining their preferences for inclusion in research can help make consent more meaningful.	Extensive participation of children in cancer trials. This study is with CHILDREN WITH CANCER. Few studies have examined the understanding of their disease and its treatment and the extent of their desire to be included in the decisions. They develop the quality-of-assent (QuAs) tool to assess which children with cancer enrolled in pediatric therapeutic oncology research protocols understand about research, their research-related treatment, and their inclusion preferences in making decisions about their watch	High

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
			treatment efficacy, generalizable knowledge, and voluntariness + 5 additional purpose of the intervention) and appreciation (1-3). The children's preference for participation research was based on their responses to 5 domains of research related decision making: Decisional priority, Types of decisions, Role in decision to enroll in protocol, Preferences / Perceptions and Suggestions, The age of 14 was selected as the evaluation point for the component related to the instrument preferences. The interviews were transcribed literally and transcripts were checked against the audio tape. Follow-up period: January 2005 - September 2007 Toll: Of 62 eligible patients, 37 completed the study	The assessment of the goal the 3 main reasons were "to help future children with cancer" (27 of 37 [73%]), "to improve personally" (22 of 37 [60%]) obtain and to help their physician to learning (43% [n = 16]). Children with Hodgkin's disease, germ cell tumors and leukemia greater knowledge and appreciation of the research than children with other cancers (P? .019 and P? .001, respectively), showing no relation to gender, age, protocol, months from the diagnosis and the termination or not of the treatment. PARTICIPATION IN DECISION-MAKING: Although all children wanted to participate in decision-making, 18 out of 37 (49%) did not have or do not remember having played a role in their decision to enroll, and 14 out of 37 (38%) they did not feel free to disagree with the inscription in the essay. The desire to make joint decisions was almost universal 97%. They felt pressured by their parents, the most common reason for signing up. Three-quarters (n = 28) would have liked to talk to other children enrolled in the research to help them understand what it means to be part of a study		out. Oral and written presentation is an effective method established to improve understanding	

REFERENCE	STUDY	INTERVENTION	RESULTS	CONCLUSIONS	QUALITY OF EVIDENCE
Short quotation: Unguru, 2009	Design: Critical review of the literature on assent. Opinion Article Goals: -Exploring the history of assent -Evaluate the central role of the evaluation of the understanding of the child -Determine the preference for participation in decisions related to your care -Describe the necessary components of meaningful assent. Period of realization: Ns	ELEMENTS OF THE ASSENT: must be independent of consent. The two concepts can not be equated. Importance that a child understands risks / benefits. To be valid, it should be contextual, taking into account the range of experiences the child experiences in the context of wider family relationships. The child's ability to make decisions must be respected. Finally, researchers should evaluate the quality and adequacy of children's understanding. CHILD'S ROLE IN THE SETTLEMENT PROCESS: Children do not need to understand the 8 components of the IC, when they agree to participate. You have to take into account what the child wants to know. Proposes the Assent Quality Questionnaire (QA) to assess what children understand and what they want to know. DECISION-MAKING MODELS: A multidimensional conceptual model, conceived of assent as a process. It establishes appropriate roles for children, parents and doctors and takes into account developmental factors, the individual and the context. Models based on autonomy, are based on adult IC and focus on competition, a legal term, rather than capacity, a term of development.	Assent strategies focus on knowledge of the child's cognitive abilities and decision-making skills. Appreciate what you understand and your preferences. It should be respected that some children feel comfortable in a limited role in decision making. Others want to be included in the decisions and expect parents to listen to them and keep them in mind. EFFECTIVE COMMUNICATION is a prerequisite for shared decision making, a strong foundation on which to base assent.	The guidelines are not intended to be universally applicable, as they require that the assent process be sufficiently malleable to accommodate the child's particular situation, family experiences and values. Guides should provide advice and a general framework. There must be consensus in key areas of assent: 1) the need to appreciate the assent from a child's point of view 2) the importance of understanding the child and that he / she prefers to participate 3) the role of medical researchers creates the possibility of a very real ethical tension, which should be honest and frank community to children and parents 4) an adequate model of assent will only be practical and applicable if it is multifaceted and flexible in its conception of families.	Low

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF EVIDENCE
Short quotation: Vitiello 2007	Design: Observational, prospective study with intervention Goals: To study the comprehension of a clinical trial in adolescents with depression (TADS Study) by means of a self-filled questionnaire at 6 weeks of randomization Period of realization: 2003	Number of participants / group: 295 adolescents aged 12-17 years (149 boys) Participating Features: The study consisted of treating adolescents with major depression with Fluoxetine, cognitive-behavioral therapy, both, or placebo (the pharmacological part was double-blind).	Intervention: Multiple answers questionnaire to see the level of understanding of IC items (12 questions, plus two open final questions on motivation to participate and level of agreement between the child and the parents). Questionnaire passed at 6 weeks of randomization. Text of the questionnaire in the article. Follow-up period: N / Not Applicable Toll: 43	High rate of correct answers: 10.3 out of 12 adolescents, and 11.2 out of 12, parents. The worst-understood item was the nature of the project: "a clinical trial" was answered only by 63.6% of adolescents and 66.5% of parents (note this low percentage and the high percentage of other questions; go all at the same time). The group that received psychotherapy was the worst understood that it was an investigation.	Good understanding of the various IC items, except for the one that refers to their nature (which is a clinical trial), especially poorly understood in the group randomized to cognitive-behavioral therapy	Good understanding of various IC items and assent in adolescents in a clinical trial for depression. It can influence the legibility of the IC	High

ANEXO 10: El uso de las redes sociales para el reclutamiento de participantes en ensayos clínicos: perspectiva de los comités de ética (CEI/CEIm)

VI CONGRESO ANCEI

TARRAGONA 2019

Trabajando juntos para mejorar el debate ético en la investigación biomédica

TARRAGONA, 30-31 DE MAYO DE 2019

LIBRO DE PONENCIAS Y COMUNICACIONES

Asociación Nacional de
Comités de Ética de la Investigación

Edita: ERGON. C/ Arboleda, 1. 28221 Majadahonda (Madrid)

ISBN: 978-84-17844-10-3
Depósito legal: M-18898-2019

C2

El uso de las redes sociales para el reclutamiento de participantes en ensayos clínicos: perspectiva de los comités de ética (CEI/CEIm)

J. Fons-Martínez[1], A.J. Quesada[2], E. Fernández de Uzquiano[3], M. Ugalde Díez[4], A. Hernández Gil[5], M. Cubillo Díaz-Valdés[6]

[1]Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (Fisabio). Valencia. [2]CEI Instituto de Salud Carlos III. [3]CEIm Hospital Universitario La Paz. [4]CEIm Hospital Universitario 12 de Octubre. [5]CEIm de Euskadi. [6]GSK. Madrid.

INTRODUCCIÓN

Estamos en un mundo que se mueve cada vez más rápido hacia las nuevas tecnologías y la investigación biomédica está creciendo en los últimos años de manera exponencial. Con ello, la ética de la investigación cobra cada vez más importancia y aspectos tan sensibles como la privacidad, confidencialidad y protección de los datos tienden a ser cada vez más estrictos.

La implantación de las redes sociales (RRSS) es cada vez mayor. La nueva legislación de protección de datos supone una mayor dificultad para llegar a un alto número de personas. La incorporación de las RRSS en el reclutamiento de potenciales participantes en ensayos clínicos (EC) es previsible y los comités de ética de investigación (CEI/CEIm) deben debatir las implicaciones de su uso.

OBJETIVO

Identificar las principales oportunidades y barreras del uso de las RRSS y nuevas tecnologías en el reclutamiento de participantes en ensayos clínicos desde la perspectiva de los CEI/CEIm.

METODOLOGÍA

La metodología llevada a cabo consiste en un grupo nominal con 5 representantes de comités de ética de investigación nacionales.

Esta metodología consta de varias fases:

- **FASE 1.** REFLEXION INDIVIDUAL Y GENERACIÓN DE IDEAS
  - Esta fase tiene una duración de 5 minutos. Se les presenta a los participantes una pregunta a la cual responden con ideas trabajadas de forma individual. Estas respuestas se apuntan en "post-its".
- **FASE 2.** EXPOSICIÓN DE LAS IDEAS
  - Se procede a leer las respuestas en voz alta, una cada vez, por turno, hasta que se acaben. Todas ellas se irán anotando.
  - No se podrán discutir las respuestas.

- **FASE 3.** DISCUSIÓN Y ACLARACIONES
  - En esta fase, se procede a aclarar los contenidos de cada "idea". No necesariamente por quien las formuló, y se genera una discusión/debate sobre ellas.
  - Se procede a agrupar las "ideas" en categorías más amplias, bien por que estén relacionadas o porque se agrupen dentro del mismo concepto/tema.
  - Es importante señalar que en esta fase no se retira ninguna idea (salvo por repetición).
- **FASE 4.** PUNTUACIÓN/PRIORIZACIÓN DE LOS ITEM
  - Esta fase consiste en hacer un ranking individual: Asignando el 1 a la categoría que se considere más relevante, el 2 a la siguiente y así sucesivamente (a mayor puntuación menor relevancia). No se puede repetir ninguna puntuación.
- **FASE 5.** CÁLCULO DE PUNTUACIÓN Y LISTADO PRIORIZADO
  - Finalmente se recoge la puntuación de cada categoría y se establece la importancia/prioridad de cada una de ellas según su puntuación.

Las preguntas que se llevaron a cabo en este *workshop* fueron 4. Con cada pregunta se repitió esta metodología de grupo nominal anteriormente explicada.

En esta comunicación se presentan y analizan únicamente los resultados sobre el uso de redes sociales para el reclutamiento (preguntas 1 y 2).

- **Pregunta 1:** ¿Cuáles son las principales barreras desde el punto de vista ético para el uso de las RRSS para reclutar participantes?
- **Pregunta 2:** ¿Cuáles son las principales oportunidades que ofrecen las redes sociales para reclutar participante?
- **Pregunta 3:** ¿Cuáles son las principales barreras desde el punto de vista ético para el uso de las nuevas tecnologías para dar la información al potencial participante?
- **Pregunta 4:** ¿Cuáles son las principales oportunidades que ofrecen las nuevas tecnologías para informar a los potenciales participantes?

Una vez se identificaron las principales barreras, se realizó una dinámica grupal para discutir cómo se podrían superar dichas barreras y sus implicaciones.

El presente documento se ha elaborado en el marco del proyecto europeo "*Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective*" (i-CONSENT), proyecto financiado por el programa marco de la Unión Europea H2020 (acuerdo de subvención nº 741856). Página web del proyecto: https://i-consentproject.eu/

RESULTADOS

Pregunta 1: ¿Cuáles son las principales barreras desde el punto de vista ético para el uso de las RRSS para reclutar participantes?

Las respuestas generadas en torno a esta pregunta se pueden observar en los *post-its* de la figura 1, donde posteriormente se agruparon en 9 categorías. Una vez hecho el ranking individual, el cálculo de puntuaciones y el listado priorizado, las categorías de mayor a menor importancia fueron:

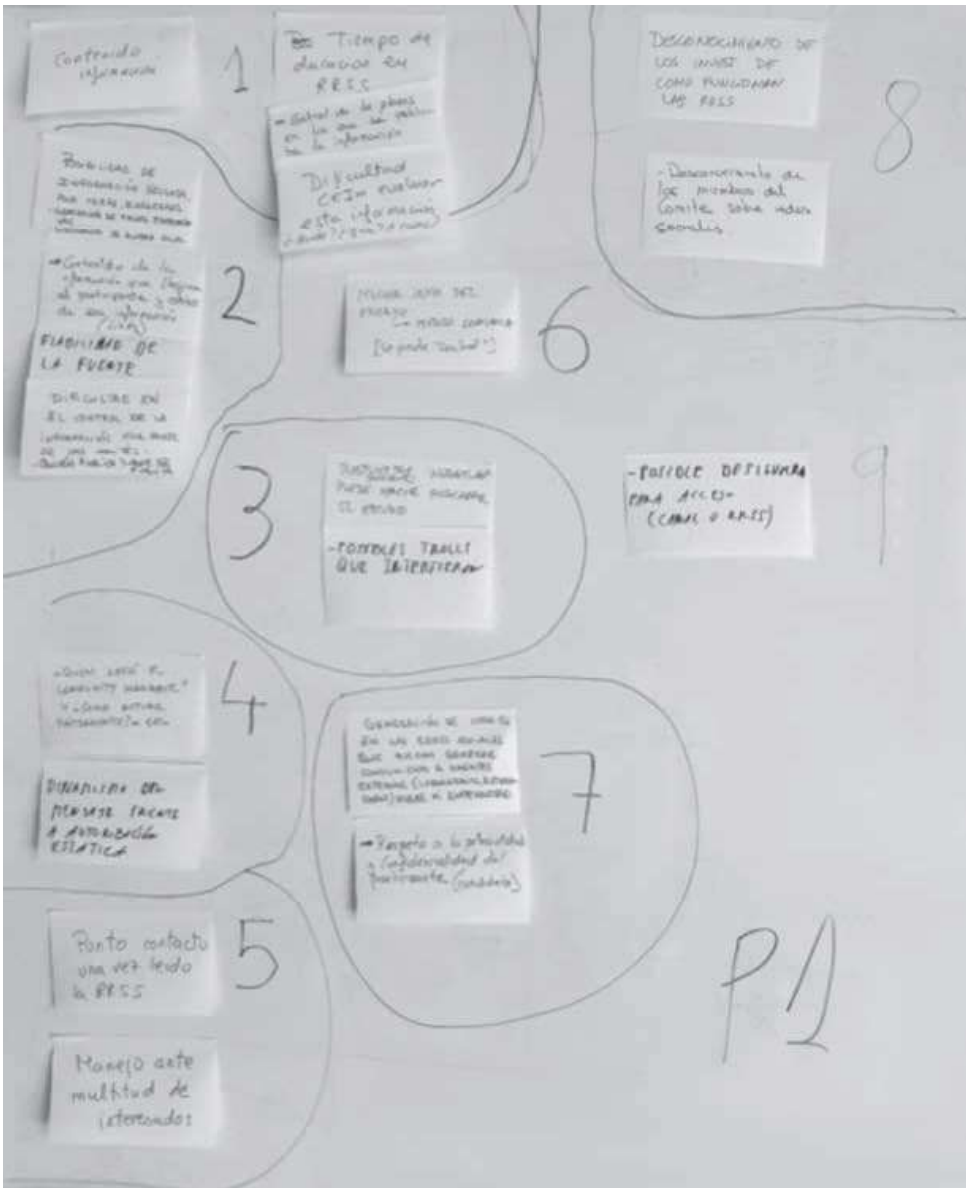


FIGURA 1. Generación de ideas de la pregunta nº 1 agrupadas en 9 categorías.

1. **Confidencialidad/Privacidad.** Respeto a la privacidad y a la confidencialidad de las personas participantes, incluyendo las posibles "cookies" que puedan generar información del participante a agentes externos como seguros médicos privados, etc.
2. **Contenido de la información (incl. Periodo de tiempo/caducidad).** Por un lado, se habló del contenido del mensaje de reclutamiento ("tweet" específico) y por otro, del contenido de la información al acceder a algún hipervínculo del "tweet" o al llamar al teléfono de contacto que lo publicite. Es importante controlar y evaluar ambos contenidos. En esta categoría también se incluyó el periodo de tiempo/caducidad que el "tweet" está publicado, valorando la posibilidad de poder borrarlo una vez que el reclutamiento haya finalizado.
3. **Fiabilidad de la fuente.** ¿Quién está publicando el mensaje? ¿Desde qué cuenta? No es lo mismo que provenga desde la cuenta oficial de la Agencia Española del Medicamento que de una persona individual. Si hubiera hipervínculos o links, ¿A dónde se redirige? ¿Es seguro?

4. **Equidad de acceso (qué tipo de RRSS, acceso a internet).** No todas las personas tienen acceso a internet y no todas las personas tienen perfiles en RRSS. Puede ocurrir que el EC se publicite en Twitter, y un usuario interesado o perfectamente elegible, solo tenga perfil en Facebook y no en Twitter. Existe, por lo tanto, un sesgo de equidad/igualdad a la hora de aproximarse a posibles participantes.
5. **"Community Manager": ¿Cómo responde? Falta de control por parte de los Comités**. Debe haber un "Community Manager" encargado del usuario de la red social que se utilice y que responda a los comentarios y controle la expansión mediática del mensaje. Una barrera por parte de los comités es que ellos pueden aprobar y evaluar el contenido del mensaje inicial, pero está fuera de su alcance las respuestas que el "Community Manager" haga posteriormente. Es decir: Dinamismo del mensaje ante una autorización estática.
6. **Poder/impacto de medios de comunicación (alarma social).** Otra barrera importante de las RRSS es el hecho de que se hace pública mucha información, al alcance de todos. Esto puede originar que la información llegue a la prensa y otros medios de comunicación y se pueda transformar, dificultando el control y pudiendo crear una alarma social sobre la vacuna o producto en investigación.
7. **Perfil y recursos de la persona encargada de contestar.** Si el contenido del "tweet" con el mensaje de reclutamiento deriva a una persona de contacto para más información, es importante saber quién va a ser esa persona de contacto: ¿Algún miembro del equipo investigador, el propio investigador, etc? Debe estar capacitada para responder a todas las preguntas del posible participante y los comités deben evaluar también este paso.
8. **Desconocimiento de las RRSS/nuevas tecnologías.** Tanto por parte de los investigadores como por parte de los miembros de los comités.
9. **Respuestas adversas/Trolls.** Uno de los riesgos al utilizar RRSS es que pueden originarse respuestas negativas que puedan hacer fracasar el estudio. Son respuestas que no se pueden evitar, ya que los comentarios en RRSS dando opinión son legítimos y legales, pero es un riesgo para el EC. Pueden aparecer grupos anti-vacunas o líderes de opinión con muchos seguidores que comenten negativamente el EC y provoquen un impacto negativo.

Pregunta 2: ¿Cuáles son las principales oportunidades que ofrecen las redes sociales para reclutar participante?

Las respuestas generadas en torno a esta pregunta se pueden observar en los *post-its* de la figura 2, donde posteriormente se agruparon en 5 categorías. Una vez hecho el ranking individual, el cálculo de puntuaciones y el listado priorizado, las categorías de mayor a menor importancia fueron:

1. **Empoderamiento (autonomía) de los posibles participantes.** Son los propios posibles participantes los que acuden libremente al llamamiento. Aumenta la autonomía de los pacientes.
2. **Transparencia.** El hecho de hacer público toda la información aumenta la transparencia y con ello la confianza.
3. **Democratización del acceso.** Se evita el sesgo donde el investigador ofrece el EC solamente a los participantes que él crea oportuno. De esta manera, hay una democratización del acceso.
4. **Educación Sanitaria.** Es una manera de promover la educación sanitaria, proporcionando información al alcance de todos sobre qué es un ensayo clínico, cómo funciona, qué implica su participación, etc.
5. **Eficiencia del reclutamiento.** En un mundo cada vez más tecnológico, el alcance de personas al que se puede llegar por RRSS es muy alto, y esto aumentaría la eficiencia del reclutamiento.

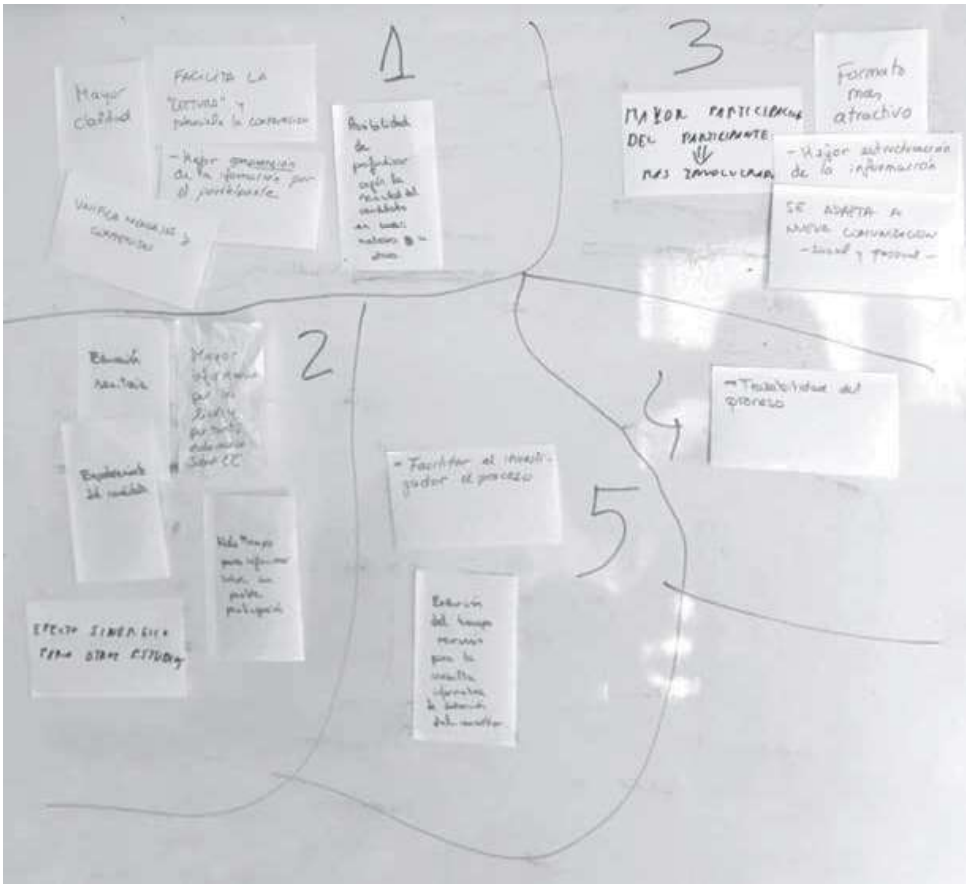


FIGURA 2. Generación de ideas de la pregunta nº 2 agrupadas en 5 categorías.

DISCUSIÓN

Oportunidades: Se concluyó que el uso de las RRSS puede mejorar la autonomía del participante, incrementando su empoderamiento, democratizando el acceso a los ensayos clínicos y mejorando la educación sanitaria. Además, se destacó la posible contribución de las RRSS en el aumento de la transparencia y de la presión para la publicación de los resultados independientemente de los intereses del promotor. Se consideró un beneficio marginal el aumento en la eficiencia del reclutamiento (llegar a más personas en poco tiempo).

Barreras: La principal barrera detectada se refirió a la confidencialidad/privacidad del potencial participante al interactuar con las RRSS y a los usos perversos que se puedan generar. Se detectó la preocupación por la dificultad de evaluar los contenidos que se van a publicar en las RRSS, el control de las interacciones que se produzcan y la fiabilidad de las fuentes utilizadas.

Se señaló la existencia de un posible impacto en los medios de comunicación ante información que aparezca y de las respuestas adversas hacia el EC en las RRSS, aunque se consideraron una barrera menor.

Se señaló la importancia de describir correctamente a los CEI/CEIm los procedimientos a seguir para continuar el reclutamiento tras el primer contacto en las RRSS.

CONCLUSIONES

La acogida de las RRSS en el proceso de reclutamiento es positiva por parte de los CEI/CEIm, pero con algunas reservas sobre las que es necesario profundizar.

De la discusión grupal sobre las principales barreras identificadas se detecta la desconfianza con las RRSS por el desconocimiento de los miembros del CEI/CEIm sobre el uso y protección de datos en RRSS, lo que sugiere la necesidad de incorporar un experto en esta materia a los comités.

BIBLIOGRAFÍA

Workshop celebrado el día 27 de marzo de 2019 en el Centro Nacional de Investigaciones Cardiovasculares (C/ Melchor Fernández Almagro, 3. Madrid). Asistentes:

1. Arantza Hernández Gil. *CEIm de Euskadi*
2. Antonio Jesús Quesada Navidad. *CEI Instituto de Salud Carlos III.*
3. Emma Fernández de Uzquiano. C*EIm de La Paz.*
4. María Ugalde Diez. *Comité Ético de Investigación Clínica.*
5. Javier Díez-Domingo. *CEI Atención Primaria Comunitat Valenciana. CEI Dirección General de Salud Pública/FISABIO. FISABIO (i-CONSENT)*
6. Jaime Fons-Martínez. *FISABIO (i-CONSENT)*
7. María Cubillo Díaz-Valdés. *GSK (i-CONSENT)*