VNIVERSITAT DE VALÈNCIA Facultat de Farmàcia

Evaluation and improvement of the quality of the discharge prescription in Cystic Fibrosis children hospitalised for intravenous antibiotic therapy.

TESIS DOCTORAL

Presentada por:

Verónica Chorro-Marí

Directores:

Matilde Merino Sanjuan, Mónica Climente Martí, David Gómez-Pastrana Durán

VNIVERSITAT DE VALÈNCIA Facultat de Farmàcia

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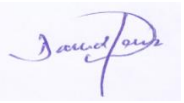
Los Doctores Matilde Merino Sanjuán, Catedrática de Farmacia y Tecnología Farmacéutica de la Universidad de Valencia; Mónica Climente Martí, Jefa del Servicio de Farmacia del Hospital Universitario Doctor Peset de Valencia y Profesora Asociado Asistencial de la Universidad de Valencia y David Gómez-Pastrana Durán, Facultativo Especialista de Pediatría del Hospital Materno Infantil de Jerez, Profesor Asociado de Pediatría de la Universidad de Cádiz y Bank Associate Specialist in Paediatric Respiratory in Barts Health NHS Trust,

CERTIFICAN QUE:

La presente memoria de Tesis Doctoral realizada por Verónica Chorro-Marí y que lleva por título "Evaluation and improvement of the quality of discharge prescriptions in Cystic Fibrosis children hospitalised for intravenous antibiotic therapy", ha sido realizada bajo la dirección compartida de los mismos y reúne todos los requisitos necesarios para su presentación, juicio y calificación.

Lo que suscriben, en Valencia, 29 de Mayo de 2017



Matilde Merino Sanjuán Mónica Climente Martí David Gómez-Pastrana

La idea de realizar mi tesis se la debo, en gran parte, a Don Víctor Jiménez, quién no sólo me enseñó su pasión por la farmacocinética sino que me mostró la esencia de la seguridad farmacoterapéutica, el camino a la calidad, a proyectar hacia la excelencia… y además porque con su entusiasmo, Don Victor fue el mayor predicador en difundir el conocimiento que jamás he conocido.

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La fórmula del valor o éxito en la vida / The equation of success in life:

$$\boldsymbol{v} = (\mathbf{c} + \mathbf{h})\, \boldsymbol{a}$$

v: valor / value; c: conocimiento / knowledge; h: habilidad / hability; a: actitud / attitude

V. Küppers

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To all of you, from the bottom of my heart, thank you!

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Abbreviations

95%CI: 95% Confidence interval
ABPA: Allergic bronchopulmonary aspergillosis
ANOVA: Analysis of variance
ATP: Adenosine triphosphate
BH: Barts Health NHS Trust
BNF: British National Formulary
CCG: Clinical Commissioning Group
CCG: Clinical commissioning group
CF: Cystic fibrosis
CFRD: CF related diabetes
CFTR: Cystic fibrosis transmembrane conductance
CNS: Clinical Nurse Specialist
CQC: Care quality commission
CRS: Clinical Record System
DIOS: Distal Intestinal Obstruction System
DL: Discharge letter
DNA: dinucleotide adenylyl
DNAse: Dornase alpha
EPR: Electronic prescribing record
EU: European Union
FDA: Food and Drug Administration
FEV_1: Forced expiratory volume 1
FP10: Primary care prescriptions
FVC: Forced Vital Capacity
GORD: Gastro-oesophageal reflux disease
GP: General Practitioner
H influenza: Haemophilus influenza
H: Hospital
HCN: High cost nebulisers
HP: Hospital Pharmacist
HTS: Hypertonic saline
I.O: Improvement opportunities
IRT: Immuno-reactive trypsinogen
IV: Intravenous

MDT: Multidisciplinary team
ME: Medication errors
NG: Nasogastric
NHS: National Health System (referring to United Kingdom's)
NMC: Nursing and Midwifery Council
NPD: Nasal potential difference
NPSA: National patient safety agency
NRLS: National Reporting and Learning Service
NSAIDs: Non steroid anti-inflammatory drugs
OR: Odds ratio
PA: *Pseudomonas aeruginosa*
PC: Primary care
PCRP: Primary care repeat prescription
PEG: Percutaneous endoscopic gastrostomy
PERT: Pancreatic enzyme replacement therapy
PK: Pharmacokinetics
PODs: Patient's own medication
POM: prescription only medicine
POSH: Patient's own supply at home
PPI: Proton pump inhibitor
RCA: Root cause analysis
RLH: Royal London Hospital
RR: Relative risk
S aureus: *Staphylococcus aureus*
SCR: Summary Care Records
TTA: To take away
UK: United Kingdom
USA: United States of America
USS: Ultrasound scan

Resumen

Evaluación y mejora de la calidad de la prescripción al alta hospitalaria de pacientes pediátricos diagnosticados de Fibrosis Quística que ingresan para tratamiento intravenoso de antibióticos en un hospital inglés.

1. Antecedentes.

La Fibrosis Quística (FQ) es una enfermedad conocida desde la edad media, aunque durante esa época no estaba descrita como tal sino más bien como un hechizo maligno. En 1943, Farber propuso el término mucoviscidosis y este término se sigue utilizando en la actualidad.

La FQ es la enfermedad hereditaria autosómica recesiva grave más frecuente en la población blanca, con una incidencia en Europa que oscila entre 1:1.353 en Irlanda y entre 1:25.000 en Finlandia, y una frecuencia de portadores de 1 por cada 25[27]. Es una enfermedad de las células epiteliales exocrinas, que se caracteriza por la producción de un moco espeso y viscoso que obstruye los conductos del órgano donde se localiza. Aunque puede afectar a la mayoría de los órganos, los más dañados son el páncreas y el pulmón, siendo la enfermedad pancreática o pulmonar la mayor causa de morbilidad y mortalidad en estos pacientes.

El gen de la FQ ha sido el primer gen humano aislado sin conocer la proteína para la que codificaba, ni disponer de claves citogénicas que permitiesen un avance rápido en su identificación.

La FQ está causada por las mutaciones en el gen CFTR[1,2], AMPc /PKA-dependiente, que codifica para una proteína conocida como CFTR (*Cystic Fibrosis Transmembrane Conductance Regulator*), que actúa como canal principal del cloro de la membrana e influye en otros iones (calcio, sodio, etc.) y suele localizarse en la membrana apical del epitelio secretor de las glándulas mucosas de vías aéreas, digestivas y reproductoras, y en las serosas del sudor y saliva.

La alteración del transporte de electrolitos, principalmente del transporte de cloruro, es la anomalía principal de la FQ, conllevando a secreciones en diversos órganos excesivamente espesas y deshidratadas, provocando la obstrucción de los conductos del páncreas, glándulas salivares, epidídimo, intestino, bronquios y bronquiolos principalmente. La formación de esas secreciones anormalmente espesas es el resultado final de un flujo alterado de iones de cloruro y de sodio, además del agua que les acompaña[3].

Cada persona hereda un gen CFTR del padre y otro de la madre, siendo una enfermedad recesiva que solo se desarrolla cuando existen mutaciones perjudiciales en los dos genes CFTR. Se han descrito casi dos mil mutaciones del gen CFTR en la base de datos de mutaciones de CFTR a disposición pública (https://www.cftr2.org/) y más de 1550 son causantes de enfermedad. Desgraciadamente, el conocimiento actual es incompleto ya que se siguen descubriendo nuevas mutaciones del gen CFTR.

Gracias a los avances de la ciencia realizados durante el siglo XX (que han permitido mejorar el conocimiento de la fisiopatología de la FQ) y al cuidado multidisciplinar que reciben los enfermos, la supervivencia de los pacientes con FQ en la actualidad supera los 40 años de edad, cuando a mediados del siglo pasado, la edad media de supervivencia no superaba el año de vida.

Los pilares del tratamiento de la FQ se basan en la nutrición, fisioterapia respiratoria, ejercicio físico, y utilización de medicamentos destinados a

paliar la sintomatología y a tratar deficiencias, como las de vitaminas y enzimas pancreáticas, a mejorar el aclaramiento de la vía aérea, o a actuar de forma profiláctica en las infecciones pulmonares como ocurre con el uso de antibióticos.

Los tratamientos farmacoterapéuticos que reciben los niños con FQ en Inglaterra se basan en:

- mucolíticos nebulizados para mejorar el aclaramiento de la vía aérea y oral en el tratamiento y prevención del síndrome de obstrucción intestinal distal;
- antiinfecciosos nebulizados, por vía intravenosa y oral;
- nutritivos de enzimas pancreáticos, principalmente vitaminas liposolubles y suplementos de iones como sodio y calcio;
- agonistas de los receptores beta (broncodilatadores);
- insulinas cuando se desarrolla diabetes causada por FQ y por el uso de fármacos antiinflamatorios;
- gastrointestinales para acelerar la motilidad intestinal en el reflujo, evitar exceso de mucosidad en el aparato digestivo y para prevenir el síndrome de obstrucción intestinal distal;
- moduladores de la proteína CFTR (solo en determinados pacientes y a partir de una cierta edad).

En Inglaterra existe amplia experiencia en la integración del farmacéutico clínico como parte del equipo multidisciplinar que atiende a los pacientes. El farmacéutico pediátrico es, en efecto, una figura clave en el equipo de pase de visita a los enfermos ingresados en planta y participa en las

decisiones clínicas encaminadas a optimizar el tratamiento farmacoterapéutico que recibe al paciente y a mejorar el grado de conocimiento que este tiene de su tratamiento y de su enfermedad, lo que contribuye por una parte a que los pacientes aumenten el grado de adherencia del tratamiento farmacoterapéutico que reciben y por otra a que se facilite, de forma temprana, la identificación de problemas relacionados con la medicación, tanto reales como potenciales.

En los niños con FQ, además de la propia complejidad inherente al paciente pediátrico, se suman otros factores que aumentan todavía más la complejidad de la farmacoterapia, tales como las múltiples potenciales interacciones farmacocinéticas o la limitada disponibilidad de formas farmacéuticas adecuadas para su administración en niños, lo que requiere el uso frecuente en este grupo de pacientes de fármacos no aprobados para su uso, con el consiguiente riesgo de errores en el proceso de prescripción. Todo lo anterior justifica la participación activa del farmacéutico clínico en el equipo interdisciplinar, trabajando de forma descentralizada en las áreas clínicas e interactuando diariamente con los pacientes y familiares, con el personal médico y de enfermería, y cuando se requiere, con fisioterapeutas, psicólogos y dietistas.

El objetivo de la atención farmacéutica proporcionada por el farmacéutico clínico integrado en el equipo multidisciplinar es contribuir a alcanzar resultados terapéuticos predefinidos que mejoren la calidad de vida del paciente y minimizando los riesgos inherentes al uso de los medicamentos[4]. Con la publicación en 1999 del informe del Institute of

Medicine (IOM), To ERR is Human: Building a safer Health System[129], se despertó en las instituciones sanitarias el ánimo de proteger al paciente y desde ese momento las publicaciones científicas relacionadas con la seguridad clínica del paciente, entre ellas, las que evalúan los errores de medicación, incrementó considerablemente. En este sentido, el estudio desarrollado en España sobre los efectos adversos vinculados con la hospitalización (ENEAS) concluye que la incidencia de efectos adversos durante el periodo del estudio fue de un 8.4%, siendo los medicamentos responsables del 37% de los casos y en la mitad de ellos estos eran prevenibles[86]. Una cultura de seguridad es indispensable en un ambiente hospitalario, en donde se debe compartir el conocimiento de errores, reales o potenciales, con el fin de evitar que alcancen al paciente. El National Patient Safety Agency (NPSA) presenta los pasos necesarios para conseguir una organización más segura donde el paciente es el centro de atención de seguridad[83]. Estos pasos están dirigidos a crear una cultura de compartir y comunicar abiertamente los errores con el fin de aprender de ellos, integrando sistemas de gestión de riesgos, de análisis de las causas y factores contribuyentes al error de medicación, con el fin de proponer las soluciones que se estimen necesarias para mitigar el riesgo de que el mismo error vuelva a ocurrir.

En la práctica clínica, un error es un fallo que causa o que podría causar daño a los pacientes tanto por práctica clínica realizada incorrectamente o por práctica clínica omitida. Según la FDA, el error de medicación es aquel evento prevenible que podría causar o que genera un uso

inapropiado del medicamento, mientras la medicación está en manos del profesional sanitario, del paciente o del consumidor. La prescripción y la administración de medicamentos son dos procesos integrados en la cadena farmacoterapéutica que tienen implícito un riesgo de error de medicación elevado. Varias organizaciones han adoptado el concepto de los 5 parámetros que deberían cumplirse en una prescripción médica (5 *rights*) para considerarla de calidad: *Right patient, Right drug, Right dose, Right route, Right time*[5]. Desde la experiencia clínica diaria en plantas de hospitalización de pediatría es importante añadir un parámetro adicional, la forma farmacéutica, y adoptar en los estudios de medicación realizados en pacientes pediátricos la necesidad de que las prescripciones reflejen de forma correcta los seis parámetros arriba indicados.

Con el fin de conocer y entender cómo ocurren y cómo se pueden prevenir los errores, se requiere disponer de una clasificación clara de los mismos. La tipificación de los errores de medicación realizada en esta Memoria se basa en dos tipos: cometidos (cuando se comete un error) u omitidos (cuando se omite cualquier parámetro imprescindible para considerar una prescripción de calidad). Y a su vez, estos se subdividen atendiendo al parámetro evaluado: fármaco, dosis, vía de administración, frecuencia, duración del tratamiento y forma farmacéutica.

Las causas de los errores definidas en los 7 pasos de la NPSA se pueden aplicar en cualquier disciplina. Así pues, las causas de los errores de medicación pueden clasificarse como educacionales, comunicativas, tecnológicas, organizativas o humanas. De esta manera, conociendo las

causas de los errores y haciendo el esfuerzo de crear una cultura de seguridad se podría alcanzar el objetivo de prevenirlos. Los 7 pasos para la seguridad del paciente se resumen en los siguientes:

1. Paso 1: crear una cultura de seguridad.
2. Paso 2: liderar y dar soporte al personal.
3. Paso 3: integrar la actividad en un manejo de riesgo con el fin de asesorar lo que ha fallado.
4. Paso 4: promocionar la comunicación de los errores.
5. Paso 5: involucrar al paciente y al público, siendo abiertos y honestos respecto al error.
6. Paso 6: aprender y compartir/difundir las lecciones de seguridad, hacienda análisis en modo de fallo.
7. Paso 7: implementar soluciones para prevenir daño.

Respecto a la calidad y seguridad de la prescripción en niños con FQ, es necesario tener en cuenta que la prescripción es el primer paso documentado de una serie de procesos que ocurren hasta que el medicamento se administra al paciente. En el sistema de salud inglés se dispone de múltiples fuentes de prescripción. Además, la documentación que se maneja en cada una de ellas es compleja en sentido logístico, pues los niños, y una gran mayoría de enfermos crónicos, no asumen el gasto de la medicación o de los tratamientos que reciben. Así pues, quienes financian los tratamientos crean sus propias redes para controlar el gasto y optimizar los tratamientos de la mejor manera posible. En consecuencia, la medicación que disponen los pacientes de FQ puede

provenir de una oficina de farmacia dispensada en atención primaria, o de una farmacia externa anexa a pacientes externos en el hospital (secundaria), de un servicio a domicilio o desde el hospital mientras el paciente está ingresado. De esta manera la conciliación de la medicación que reciben estos pacientes, afectados de patologías crónicas, siempre polimedicados y de alto coste para el sistema de salud, en el ingreso hospitalario, es un reto.

Cuando un paciente requiere una asistencia que conlleva un cambio de nivel asistencial (por ejemplo: el paciente requiere un ingreso hospitalario, o el paciente ingresado cambia de planta médica, entre otros) está más expuesto a errores de medicación. Si a este hecho se añade el factor pediátrico (dosis ajustada por peso/edad, distintas formas farmacéuticas con distinta biodisponibilidad, etc.) y una enfermedad crónica, que tiene patologías asociadas tratadas todas ellas con diferentes fármacos, la probabilidad de errores de medicación se incrementa y puede alcanzar un alto valor cuando la frecuencia de ingresos hospitalarios de los pacientes para recibir tratamiento por vía intravenosa es elevada. Estas circunstancias ponen de relieve la importancia de disponer para este grupo de pacientes de una prescripción médica al alta hospitalaria de elevada calidad, ya que este documento debería ser el de referencia para el paciente además de garantizarle una farmacoterapia segura y de calidad.

2. Objetivos.

Objetivo general:

Mejorar la calidad de la prescripción al alta hospitalaria en el paciente pediátrico diagnosticado de fibrosis quística que ingresa para tratamiento intravenoso mediante la utilización de indicadores de seguridad.

Para ello el estudio se ha realizado en dos periodos, uno retrospectivo y otro prospectivo, teniendo en cada uno de los periodos los siguientes

Objetivos específicos

Fase retrospectiva:

- Evaluar de forma cualitativa y cuantitativa los errores de medicación en las prescripciones al **alta** hospitalaria validadas por el farmacéutico.
- Evaluar de forma cualitativa y cuantitativa los errores de medicación en los informes médicos emitidos en el **alta** hospitalaria.
- Identificar, tipificar y analizar las causas de los errores de medicación detectados con mayor frecuencia.
- Proponer recomendaciones de mejora a los profesionales implicados y diseñar estrategias para implementar dichas recomendaciones en la práctica asistencial.

Fase prospectiva:

- Evaluar de forma cualitativa y cuantitativa los errores de medicación en el **ingreso** hospitalario de los pacientes.
- Evaluar de forma cualitativa y cuantitativa los errores de medicación en las prescripciones al **alta** hospitalaria tras validación por el farmacéutico.
- Evaluar el impacto de las recomendaciones de mejora realizadas.

3. Material y Métodos

3.1. Pacientes, criterios de inclusión y ámbito del estudio.

Pacientes pediátricos diagnosticados de FQ que ingresan en la planta de respiratorio del hospital Royal London para recibir antibioticoterapia intravenosa. El hospital de estudio es uno de los Hospitales del Sistema de Salud Publico del grupo Barts Health NHS.

La propuesta de estudio se valoró y autorizó por la unidad de efectividad clínica de Barts Health NHS Trust (el número de identificación del estudio otorgado fue: 7080).

3.2. Fases del estudio.

Una primera fase retrospectiva de dos años de duración, desde Enero de 2013 a Diciembre de 2014.

Una fase de presentación de resultados al Departamento de Neumología infantil del Royal London Hospital destinada a definir y acordar estrategias de mejora (3 meses de duración).

Una fase prospectiva realizada desde mayo a diciembre de 2016 (8 meses).

3.3. Fuentes de información.

A continuación se resumen las siete fuentes de información utilizadas para realizar el estudio:

1. EPR, referente a "*electronic patient's records*", donde se encuentra la prescripción electrónica utilizada al alta hospitalaria durante los años 2013 y 2014.
2. Informe médico de alta, documento de texto donde se explican los acontecimientos ocurridos durante la estancia del paciente en el hospital (motivo de ingreso, tratamiento recibido, gérmenes identificados, espirometría, etc.) y el listado de medicamentos al alta. El informe de alta se refiere a las siglas DL, correspondientes a "*discharge letter*".
3. CRS, las siglas se refieren a "*clinical record system*", donde se encuentra la prescripción electrónica utilizada al alta hospitalaria durante el periodo del estudio prospectivo.
4. SCR, se refiere a "*summary care records*", es la prescripción electrónica de Atención Primaria que realiza el médico de cabecera.
5. PODs, siglas utilizadas para "*patient's own drugs*", la medicación del paciente, que en Inglaterra por ley debe de tener una etiqueta con la información de lo que se ha prescrito, a quién, cuando, por

quién, dónde e instrucciones de cómo y cuándo preparar, administrar o tomar la medicación.

6. Hoja de tratamiento hospitalario, donde se prescribe la medicación que el paciente debe de recibir mientras está ingresado (referente a *drug chart*).
7. Prescripciones del servicio a domicilio, que es un servicio contratado por el hospital con el fin de reducir el coste de los fármacos utilizados en FQ más caros, generalmente antibióticos nebulizados.

3.4. Variables estudiadas.

Se estudiaron un total de 30 variables, algunas comunes en ambas fases del estudio y otras exclusivas de una fase u otra. La tabla siguiente resume las variables estudiadas.

Tabla 1. Variables estudiadas: denominación y fase en la que se estudian.

Variables relacionadas con	**Numeración y denominación de la variable**	**Fase análisis de la variable: Retrospectiva (R) Prospectiva (P)**
El paciente	0- Número hospitalario	R,P
	1- Edad	R,P
	2- Género	R,P
	3- Número de patologías asociadas	R,P
	4- Tipo de patologías asociadas	R,P
	5- Si la lengua materna de los padres es inglés	P
	6- Si el niño vive con ambos padres	P
La estancia hospitalaria	7- Motivo de ingreso	R,P
	8- Número de días de estancia hospitalaria	R,P
	9- Día de la semana del ingreso	P
	10- Día de la semana del alta	R,P
La farmacote-rapia	11- Documentación de peso	R,P
	12- Documentación de alergias	R,P
	13- Coincidencia de alergias documentadas en Atención Primaria	P
	14- Tipo de fármacos	R,P
	15- Medico prescriptor	R,P
	16- Farmacéutico que valida la prescripción	R,P

	17- Cargo o experiencia del farmacéutico	R,P
	18- Existencia del informe de alta	R
	19- Fecha del día de alta	R
	20- Número de discrepancias en el informe de alta respecto a EPR	R
	21- Número de fármacos prescritos	R,P
	22- Número de fármacos prescritos con nombre comercial	R
	23- Prescripción desde Atención Primaria de tratamientos nebulizados de alto coste	P
Las estrategias de mejora.	24- Número fuentes de información para reconciliar medicación	P
	25- Número de tarjetas recordatorias para prescripción al alta	P
	26- Número de intervenciones farmacéuticas y tipo	P
	27- Número de intervenciones farmacéuticas aceptadas	P
	28- Número de altas previamente listadas por el técnico de farmacia	P
	29- Necesidad de comunicarse con Atención Primaria	P
	30- Comunicación realizada	P

EPR: Electronic prescription used in the retrospective fase.

3.5. Oportunidades de mejora.

Las oportunidades de mejora (OM) (I.O, para las siglas de "improvement opportunities") se definieron como cualquier circunstancia que causa o que podría causar un error de medicación alcanzando o dañando al paciente debido a información incorrecta o a la falta de información que se produce durante el proceso de prescripción.

Las I.O se analizaron en ambas fases del estudio en la prescripción electrónica al alta. Además, en la fase retrospectiva se analizaron en el informe médico de alta hospitalaria (DL) y en la etapa prospectiva en la conciliación de tratamientos realizada al ingreso.

La clasificación de las OM se realizó según si se trataba de errores relacionados con el procedimiento de prescripción (omisión del peso, las alergias o la firma del prescriptor); o si se trataba de errores de medicación, por información incorrecta u omitida en alguno de los seis parámetros considerados imprescindibles en una prescripción segura y de calidad.

3.6. Errores de medicación.

Los errores de medicación (ME) se definieron como cualquier incidente que podría causar o que causó daño al paciente por el uso inapropiado de fármacos debido a una prescripción incorrecta o incompleta, durante la estancia hospitalaria o al alta a domicilio.

La tipificación de los ME se resume en el capítulo de antecedentes y se describe en la siguiente Tabla 2.

Tabla 2. Descripción de tipos y subtipos de errores de medicación.

	Cometidos: información incorrecta en la prescripción	**Omitidos:** omisión de la información
Fármaco	• Incorrecto. • Continúa el tratamiento cuando se debería de haber parado. • Interacciones o problemas de absorción entre dos o más fármacos prescritos conjuntamente, que afectan la eficacia o pudiendo causar problemas de medicación (por ejemplo itraconazol junto con inhibidores de la bomba de protones,).	• El nombre del fármaco prescrito en EPR no aparecía en la carta del informe de alta (DL) o viceversa. • La farmacoterapia regular del paciente no estaba prescrita (antibióticos nebulizados, insulinas, etc). • Evidencia en la que el paciente debería de tener terapia de rescate prescrita en primaria.
Dosis	• Dosis se prescribía en volumen o con unidades erróneas (se excluyo en estos casos: AquADEKs®, Sytron® y Lactulosa). • Cuando la dosis por edad/peso prescrita era un 20% mayor o menor del que correspondía.	• Dosis o unidades omitidas en la prescripción. • Dosis que indicaran "Tómelo como lo he indicado". Se excluyo las pancreatininas enzimáticas y pomadas o medicación que no tenía que ver con FQ o alguna de las patologías asociadas del niño/a.
Frecuencia	• Cualquier frecuencia mayor o menor del 20% de lo que se esperaría para la edad/peso.	• Frecuencia omitida o indicado "cuando lo necesite" pero sin indicar la posología máxima diaria que se puede administrar.
Duración	• La duración prescrita era incorrecta.	• Antibióticos orales o nebulizados o cortisona estaban prescritos sin indicar el tiempo de tratamiento. • Nueva medicación prescrita sin indicar una fecha de revisión del fármaco.

Forma farmacéutica	• Forma farmaceútica incorrecta. • Formulación no accesible para el paciente. • Existían preparaciones más económicas que el paciente podría tomar. • Formulaciones inconsistentes para un mismo niño. • Prescripción de pastillas en niño en el que se conoce que no las puede tragar	• No se indicaba la presentación farmacéutica y existen varias comercializadas (referente a soluciones orales). • Ausencia de prescripción de tratamiento nebulizado, inhalador o insulina.
Vía admi-nistracion	• Si era incorrecto. • Si era inconsitente con otros fármacos prescritos que normalmente utilizarían la misma vía.	• Cuando se había omitido.

EPR: Electronic prescription used in the retrospective fase; DL: Discharge letter

3.6.1. Causas y gravedad de los errores

Las causas de los errores se dividieron en 5 categorías:

- Tecnológicas.
- Oganizativas (del Sistema de salud).
- Comunicativas.
- Educativas (al personal sanitario o al paciente y/o cuidador).
- Humanas.

La gravedad de los errores se clasificó según la escala de gravedad definida en el método de atención farmacéutica IASER©. Este método utiliza una escala tipo Likert en la que se otorgan cinco valores de escala ordenados de menor, cuando la gravedad del error no causaba daño de signos vitales pero se requirió monitorización (1), a mayor gravedad (5) en el que el error causa la muerte del paciente.

3.7. Conciliación de tratamientos

Se evaluó en el ingreso hospitalario durante la etapa prospectiva del estudio y al alta hospitalaria en ambas fases del estudio.

Se analizó la existencia o no de discrepancias (al ingreso y al alta) y en caso de que las hubiera se investigó si estaban justificadas o no. Cuando las discrepancias no estaban justificadas se consideraron errores de medicación (también llamados errores de conciliación).

3.8. Estrategias de mejora y acciones de seguridad.

Los resultados obtenidos en la fase retrospectiva del estudio se presentaron al Departamento de Neumología infantil del Royal London Hospital y con el objetivo de mejorar la calidad de la prescripción al alta de los pacientes de estudio se definieron y acordaron las siguientes estrategias:

1. Elaborar el informe médico de alta hospitalaria a partir de la prescripción electrónica al alta realizada por el médico y validada por el farmacéutico.

2. Diseñar una tarjeta destinada a añadirse a la hoja de tratamiento en la que se incluyeran los errores detectados con mayor frecuencia en la fase retrospectiva del estudio.

3. Realizar la conciliación de medicamentos en el ingreso hospitalario de los pacientes utilizando un mínimo de tres fuentes de información.

4. Monitorizar las intervenciones realizadas por el farmacéutico durante la estancia hospitalaria de los pacientes que estaban documetadas en la hoja de tratamiento (drug chart).

5. Incorporar personal de refuerzo (técnico de farmacia) en el proceso de la validación técnica de la prescripción médica al alta hospitalaria.

6. Comunicar al equipo multidisciplinar de Atención Primaria los cambios requeridos en el tratamiento farmacoterapéutico de los

pacientes durante la estancia hospitalaria que implicaran una modificación de la prescripcion de primaria.

3.9. Indicadores de calidad.

Los indicadores de calidad se diseñaron para evaluar la calidad de la prescripción al alta (fases retrospectiva y prospectiva) así como para evaluar el impacto de las acciones de mejora implantadas en la fase prospectiva del estudio.

Estos indicadores se crearon considerando la medicación necesaria, para que los órganos afectados con mayor frecuencia en los pacientes con FQ estuvieran tratados correctamente de acuerdo a su situación clínica, con dosis individualizadas óptimas según edad/peso.

Se definieron 19 indicadores de calidad: unos característicos de la prescripción al alta hospitalaria que se evaluaron y compararon en ambas etapas del estudio (1-11) y otros exclusivos de la fase retrospectiva: los relacionados con aspectos administrativos de la DL (12-13) o los de la fase prospectiva: los relacionados con las acciones de mejora (14-18). El indicador 19 es un indicador de calidad global de la prescripción que se fundamenta en los 5 parámetros que debería reunir una prescripción para considerarla de una calidad óptima, además de un sexto que se ha considerado muy importante en la población pediátrica, la forma farmaceutica (6-11).

La nomenclatura utilizada para los indicadores de calidad, los valores considerados como estándar en este estudio y las fases del estudio en las

que se han evaluado se resumen en la siguiente Tabla 3 (ver también las Tablas 3.6-3.9).

Tabla 3. Descripción de los indicadores de calidad con su valor estándar y fase del estudio se aplicaron.

Indicador calidad; Qi (descripción)	**Valor Standard (%)**	**Retrospectivo (R) Prospectivo (P)**
Qi 1 (identidad)	100	R, P
Qi 2 (peso registrado)	80	R, P
Qi 3 (alergias registradas)	80	R, P
Qi 4 (vitaminas prescritas)	80	R, P
Qi 5 (enzimas pancreáticos prescritos)	80	R, P
Qi 6 (fármaco)	90	R, P
Qi 7 (dosis)	90	R, P
Qi 8 (frecuencia)	90	R, P
Qi 9 (forma farmacéutica)	90	R, P
Qi 10 (vía de administración)	90	R, P
Qi 11 (duración)	90	R, P
Qi 12 (informe de alta)	80	R
Qi 13 (fecha/retraso informe de alta)	80	R
Qi14 (reconciliación al ingreso, variable 24)	80	P
Qi 15 (cartilla recordatoria, variable 25)	80	P
Qi 16 (intervenciones aceptadas, variable 27)	80	P
Qi 17 (técnico farmacia, variable 28)	60	P
Qi 18 (comunicación con primaria, variable 30)	80	P
$Q_{i_{19}}^{EPR\ or\ CRS}$ (calidad y seguridad global)	50	R, P

EPR, CRS: prescripción electrónica en la fase retro y prospectiva respectivamente.

3.10. Análisis estadístico

En el proceso de recogida y análisis de datos se ha utilizado el programa Excel 2013®. Para comparar las proporciones se han utilizado las pruebas estadísticas Chi cuadrado y para conocer la magnitud de la diferencia se calculó el Odds ratio o el riesgo relativo. Las variables continuas se compararon con las pruebas estadísticas t student o ANOVA.

Se ha considerado significación estadística cuando $p<0.05$.

4. Resultados

La población incluida en ambas fases del estudio no presentó diferencias estadísticamente significativas en género, edad, tiempo de estancia hospitalaria, número de fármacos prescritos al alta, días de la semana de alta y la mayoría de patologías asociadas. Se encontraron diferencias estadísticamente significativas en la enfermedad hepática como patología asociada ($p=0.0255$) y en el motivo de ingreso de los pacientes incluidos en las dos fases del estudio, donde el ingreso por exacerbación fue del 45.00% en la fase retrospectiva y del 63.63% en la fase prospectiva ($p=0.027$).

Se encontraron más niñas ingresadas para recibir tratamiento con antibióticos por vía intravenosa, siendo esta proporción niño/niña significativa en ambas fases del estudio ($p<0.001$ en la retrospectiva y $p=0.030$ en la prospectiva).

En la fase retrospectiva se comparó el sistema electrónico de prescripción al alta (EPR) y uno de texto libre (informe de alta). La detección de oportunidades de mejora de prescripción fue significativamente mayor en el sistema de texto libre al valorar el porcentaje del número de episodios de alta ($p<0.001$).

Al comparar las OM en ambas fases del estudio se detectaron de forma significativa menor porcentaje de pacientes y de altas con OM en la fase

prospectiva. Sin embargo, el porcentaje de fármacos prescritos con OM fue significativamente mayor en la fase prospectiva.

Al analizar las tasas de OM por paciente y por alta no se encontraron diferencias significativas entre los dos periodos aunque la tasa de OM analizada en base a cien fármacos prescritos, sí fue significativamente mayor en la fase prospectiva ($p<0.001$).

El porcentaje de altas validadas por el farmacéutico tuvo menos OM en el estudio prospectivo (81.18% en la fase retrospectiva y 52.00% en la fase prospectiva, $p<0.001$).

En la fase retrospectiva el porcentaje global (cometidos y omitidos) de errores de medicación detectados en la prescripción electrónica al alta hospitalaria (EPR), fué similar (47% omitidos y 53% cometidos), destacando el subtipo de errores cometidos mas frecuentes los de dosis (43.59%) y errores omitidos de fármaco (40%). Mientras que los errores de medicación encontrados en el informe de alta fueron mayoritariamente por omisión (84% omitidos vs 17% cometidos), sobresaliendo los errores de dosis como errores cometidos en un 47.27% y errores de omisión de forma farmacéutica en un 35.97%.

Al comparar los errores encontrados en la prescripción electrónica al alta de la fase prospectiva con la del periodo retrospectivo (EPR), se encontraron menos errores de fármaco, dosis, duración/clarificación de tratamiento en la fase prospectiva ($p<0.001$). Asímismo, los errores de forma farmacéutica fueron ligeramente menores en la fase prospectiva

del estudio. Sin embargo, la frecuencia de error de vía de administracion fue menor en la fase retrospectiva ($p<0.001$).

Respecto al subtipo de errores comparando ambas fases de estudio, los errores cometidos fueron más frecuentes en la fase retrospectiva ($p<0.05$), pero los de omisión lo fueron en la prospectiva ($p<0.05$), principalmente por omisión de la vía de administración.

La causa más probable de error en la fase retrospectiva del estudio podría atribuirse a la organización del Sistema, mientras que en la fase prospectiva la causa más probable de error puede tener origen tecnológico.

Los errores de medicación detectados en la fase prospectiva al ingreso fueron principalmente por omisión de fármacos y dosis incorrecta.

Respecto a las estrategias de mejora y de seguridad implantadas en la fase prospectiva previas a la prescripción de alta:

- Todas las hojas de tratamiento tuvieron incorporadas la cartilla recordatoria (prompt card).
- Se encontraron oportunidades de mejora al ingreso hospitalario en la hoja de tratamiento en un 65.45% de los casos y en un 70.91% en la prescripción de atención primaria.
- Se observaron un total de 134 intervenciones documentadas en las hoja de tratamiento, mayoritariamente de tipo correctivo de modificación de dosis, aceptandose un 98.53% de ellas.

El valor de los indicadores de calidad global de la prescripción al alta durante la fase retrospectiva del estudio fue 22% para la prescripción electrónica (EPR) y 9.21% para el informe de alta (DL). Este indicador alcanzó el valor de 41.82% en la fase prospectiva (CRS) (p=0.010). No se alcanzó en ninguna de las fases del estudio el valor predefinido como estándar de calidad de la prescripción (50%).

Los indicadores de calidad de la prescripción que mejoraron significativamente en la fase prospectiva fueron los de fármaco (Qi 6), dosis (Qi 7), frecuencia (Qi 8), vía de administración (Qi 10) y duración de tratamiento (Qi 11), (p<0.05).

A continuación, en la siguiente figura se resumen los valores de los indicadores de calidad obtenidos en ambas fases del estudio.

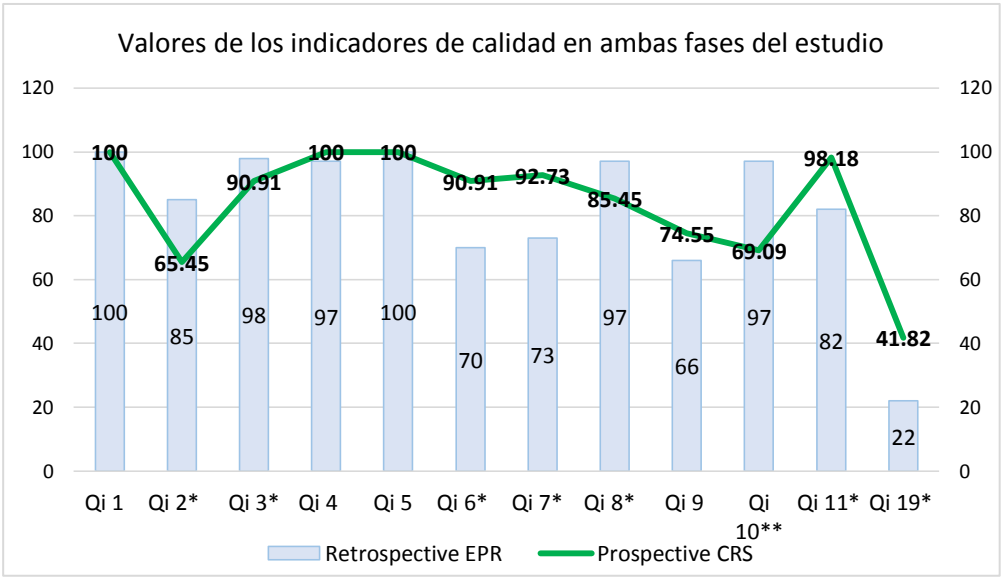


Figura 1. Valores de los indicadores de calidad.

5. Discusión

El programa de calidad descrito se podría considerar un programa de monitorización de errores de medicación y de otras oportunidades de mejora de la prescripción de medicamentos al alta hospitalaria, así como un estudio de seguimiento del impacto en la seguridad del paciente derivado de una mayor integración del farmacéutico en el cuidado del paciente pediátrico con FQ. El estudio permitió evaluar la calidad global de la prescripción al alta hospitalaria en ambas fases del estudio de investigación realizado, retrospectiva y prospectiva, permitiendo evaluar el impacto de las diferentes estrategias de mejora y acciones de seguridad implantadas.

Sin embargo, se detectan más errores de la prescripción en la fase prospectiva, a expensas de un mayor número de errores por omisión de vía de administración, cuya causa se encuentra en las particularidades del sistema informático implantado durante esta fase del estudio.

La literatura disponible relacionada en estudios similares al realizado es escasa y en algunos casos los resultados de esta Tesis contradicen los obtenidos en otras investigaciones[6] en las que se concluye que la utilización de sistemas informatizados de prescripción reducen los errores de medicación. Sin embargo, en este estudio el sistema informático utilizado en la fase prospectiva parece ser la principal causa de las omisiones de la forma farmacéutica y de la vía de administración detectadas en la prescripción, ya que la aplicación informática carece de un campo exclusivo para realizar el registro de estos parámetros de tal

forma que alerte al prescriptor en caso de que no se haya completado. No obstante, a pesar de esta limitación del sistema informático, el número total de errores de medicación cometidos (no omitidos) durante la fase prospectiva fue menor. Este resultado puede interpretarse como una mejora de la calidad de la prescripción durante la fase prospectiva del estudio que puede atribuirse, al menos en parte, al impacto de las estrategias de mejora de la calidad y de seguridad definidas tras el análisis de los resultados de la fase retrospectiva del estudio e implantadas durante la fase prospectiva del mismo. Sin embargo, la mejora de la calidad observada en la fase prospectiva no puede atribuirse únicamente a las estrategias de mejora implementadas, ya que otros aspectos que subyacen en el cuidado del paciente pediátrico diagnosticado con FQ y otros factores no cuantificados en este estudio, entre ellos los relacionados con el grado de experiencia del farmacéutico integrado en la planta de respiratorio en esta fase, no pueden deslindarse del resultado final.

6. Conclusiones.

1. Los indicadores utilizados para evaluar la calidad de la prescripción al alta hospitalaria de los pacientes pediátricos diagnosticados de fibrosis quística durante la fase retrospectiva del estudio no alcanzan el estándar de calidad definido (50%), siendo mayor la calidad de la prescripción electrónica (22%) que la calidad del informe médico del alta hospitalaria (9.21%). Esta diferencia de valores realza la importancia de utilizar un sistema de prescripción que integre campos diseñados para registrar la

información específica de los seis parámetros fundamentales de la prescripción (fármaco, dosis, frecuencia, duración de tratamiento, forma farmacéutica y vía de administración).

2. En la fase retrospectiva del estudio el porcentaje de errores de medicación, cometidos y omitidos, detectados en la prescripción electrónica al alta hospitalaria, fué similar. Sin embargo, en los informes médicos de alta hospitalaria los errores de medicación omitidos se realizaron en mayor proporción. Los tipos de errores de medicación más frecuentes en la prescripción electrónica fueron de forma farmacéutica seguidos de fármaco y dosis, mientras que en el informe médico al alta hospitalaria fueron tambien por forma farmacéutica aunque seguidos de dosis y de vía de administración.

3. Los factores contribuyentes a los errores de medicación registrados en la fase retrospectiva del estudio a partir de la prescripción electrónica y del informe médico al alta hospitalaria pueden asociarse a factores relacionados con la organización del sistema.

4. Las estrategias de mejora implantadas tras el análisis de errores de medicación detectados en el estudio retrospectivo estuvieron dirigidas a mejorar la organización del proceso de prescripción, mejorando la conciliación del tratamiento al ingreso y al alta hospitalaria, así como la integración del farmacéutico en el equipo multidisciplinar que atiende al paciente pediátrico diagnosticado de FQ.

5. En la fase prospectiva del estudio los errores de medicación detectados con mayor frecuencia en el ingreso hospitalario del paciente fueron por

fármacos omitidos, seguido de dosis incorrecta. Sin embargo, en el alta hospitalaria los errores de medicación más frecuentes fueron por omisión de la vía de administración seguidos de incorrecta frecuencia. En esta fase, las principales causas contribuyentes a cometer los errores de medicación fueron de naturaleza tecnológica.

6. En la fase prospectiva del estudio, realizada tras la implantación de las recomendaciones de mejora diseñadas, el porcentaje de altas con oportunidades de mejora detectadas en el proceso de validación farmacéutica de las prescripciones refleja un incremento significativo en la calidad tras observarse una reducción del 29.18% en el porcentaje de oportunidades de mejora detectadas en el proceso de validación farmacéutica de las prescripciones tras el alta hospitalaria (81.18% de OM en el periodo retrospectivo, 52% de OM en la fase prospectiva).

7. La formación de equipos multidisciplinares que integren profesionales expertos clínicos (médicos y enfermeros) y expertos en el uso de los medicamentos (farmacéuticos y técnicos en farmacia) facilita la toma de decisiones clínicas que aumentan el estándar de calidad en el cuidado del paciente pediátrico diagnosticado de FQ. Estas mejoras repercuten en la optimización de la farmacoterapia, en el grado de aceptación de las actuaciones farmacéuticas durante la estancia hospitalaria de los pacientes y podrían contribuir a mejorar la adherencia al tratamiento farmacoterapéutico por parte del paciente.

8. Los indicadores utilizados para evaluar la calidad de la prescripción médica de pacientes pediátricos diagnosticados de fibrosis quística

indican que la implantación de las medidas correctoras diseñadas en este estudio ha contribuido a una mejora del proceso (22% en la fase retrospectiva vs 41.82% en la fase prospectiva). No obstante, a pesar de la mejora cuantificada el valor del indicador de calidad utilizado no alcanza el estándar definido (50%). Este hecho pone de relieve la necesidad de potenciar, mantener y mejorar las estrategias de seguridad iniciadas para alcanzar las cotas de calidad deseadas.

1. Introduction

1.1. Sixty five roses

The term "65 Roses" is synonymous with the history of cystic fibrosis (CF). In the 1960s, Ricky Weiss, a four-year old with cystic fibrosis, overheard his mother, Mary, talking on the phone. As a mother of three sons with CF, Mary was making phone calls to gather support for CF research. Ricky, confronted his mother and told her that he knew about her calls. His mother was surprised, because she had kept any knowledge of the condition hidden from her sons. Confused, mum asked Ricky what he thought the phone calls were about, to which he answered "You are working for 65 Roses".

Needless to say, his mother was incredibly moved by his innocent mispronunciation of cystic fibrosis, as have many since who hear the story. Since then, the term "65 Roses" has been used by to help children put a name to their condition.

1.2. Background

Only a few decades ago having a conversation about cystic fibrosis was rare. The gigantic steps that we have seen in the lasts decades in medicine and pharmacology show how far we have come with what was a disease that initially never reached the adult stage.

Although a true documented history of CF did not exist until well into the 1930s there were observations found in a German manuscript from the

15th century (*Codex Latinus Monacensis 849*) warning "Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die".

A few other references have been found in medical texts as early as 1595 that linked salty skin and damage to the pancreas with death in childhood of infants who were "hexed" or "bewitched"[7]. The German folklore code with the blessing against the enchanted children "Wilder elbe" suggested licking the child's nose (supposedly enchanted) to find out if there was a salty flavour or not "so sint es dy elbe".

These are the first known documentations that relate the salty flavour and a disease, now known as Cystic Fibrosis (CF).

In 1606 a Professor in Medicine in a Spanish University, Dr Juan Alonso y de los Ruyzes, wrote in his book "Diex privilegios para mugeres prenadas" (Ten privilieges for pregnant ladies) that witched people were found after scratching the front brow then noticing a salty flavour in the fingers". This is another reference to the salt and curse.

Most likely the first macroscopic anatomopathological description of CF was done by Peter Paaw in 1595 in Leiden, after an autopsy of an 11 years old girl. He described "the girl was supposedly cursed; she had strange symptoms for 8 years and was skinny and was exhausted due to prolongued fever". "Pancreas was swollen, cirrotic and was bright white". "The cause of dead was the pancreas", concluded Paaw.

Nils Rosen von Rosenstein (1706-1773), a Swedish paediatrician in his book about children disease described a symptom called “fluxux coeliasus” characterised of diarrhoea, distrophia, weakness, lack of thriving despite good appetite. He described dilated hands and feet and distended abdomen and hard pancreas. These were likely his CF patients.

Carl Von Rokitansky described in 1838 the results of a 7 months old foetus autopsy, with a thin intestine perforated and meconium flow in the peritoneal cavity with an inflammatory reaction. Possibly this was what we now know as a meconium ileum.

In 1850 Alois Bednar in Viena described a similar case in a newborn that died after six days of life. Around the same time there were similar descriptions in England.

The earliest paper written about CF was produced in 1934 Dr Fanconi, a Swiss pediatrician. According to the webpage AboutCysticFibrosis.com, in a thesis written under his direction, Dr. Fanconi referred to CF as “celiac syndrome”, based on how celiac syndrome starts as a digestive disorder that interferes with the absorption of nutrients.

There was much written about medical findings in the 1930s, that in hindsight can be assumed to have been factors of CF in patients. However, the first person to give this disease the name of cystic fibrosis was Dr. Dorothy Andersen, a pathologist at Babies’ Hospital at the Columbia-Presbyterian Medical Center in New York. While conducting an autopsy on a child who showed the clinical picture of celiac disease, Dr. Anderson noted a lesion in the pancreas. Subsequently, she performed

an extensive search of the autopsy records and related medical literature, and discovered a clear, though previously unrecognised, disease pattern, which she referred to as "cystic fibrosis", as stated on the National Library of Medicine website.

Based on her findings, Dr. Anderson wrote a paper in 1938 entitled "Cystic fibrosis of the pancreas and its relation to celiac disease", which stated that out of 49 patients she studied, "in 45 of the cases, the pancreas presented a microscopic picture which is described by the term cystic fibrosis," as noted at CFMedicine.com. This writing also described intestinal obstruction in newborns, as well as intestinal and respiratory complications.

In the 1950s, pathologist Martin Bodian wrote of Dr. Anderson's paper "such a clear account of the symptoms, that it enabled many cases to be recognized that had hitherto been missed". For first time this author described the focal biliar cyrrosis, a patognomonic lesion of CF in the liver[8].

Around the same time Di' Sant Agnese, confirmed the abnormal elimination of the Chloride via sweat, which was the base of the sweat test[9].

In 1956 Bishop & Koop's ileostomy technique[10] allowed saving lifes of new borns with meconium ileum.

Soon in 1959 the chloride technique was modified by Gibson & Cook with pilocarpine[11], which so far it is one of the diagnostic techniques currently

used. Furthermore, Schwachman was the first investigator who published that not all patients had a pancreatic insufficiency and established a gravity clinical evaluation system[12] that is in current use.

Later in 1965 Noblett used Gastrografin® in non-complicated meconium ileum permitting a cure in babies without surgical intervention[13].

Other pharmacological progress like penicillin and pancreatin enzymes, for instance were a positive contribution to push the disease to longer age survival.

The key in the investigation of CF was in 1983 when Quinton discovered that the specific defect of the CF was a defect of chloride in the epithelial glans[14].

Nowadays, with the advanced technology identifying genes, medicine evidence base and the different type of treatments available the way the experts look at the disease is totally different than few years ago. And of course the approach taken today by professionals without any doubt is more optimistic than before.

Significant improvement in the survival of patients with CF has been achieved in the last decades.

Obviously, this is only possible when there is a good understanding of the disease and its infections as well as prompt diagnosis with neonatal screening, timely and aggressive nutritional support, physiotherapy, pharmacotherapy initiation and its adherence amongst others factors.

Treatment at a specialized CF center by a multidisciplinary (MDT) dedicated team, including frequent visits, and periodic routine tests are essential to detect and treat early changes. Adherence to these therapies is challenging and it should be discussed with the patients at every clinic visit[15].

Due to the complex pharmacology to which CF children are daily exposed and the importance of medicines optimisation it is crucial to have accurate up to date information of the pharmacological treatment a child is on.

Furthermore, as children grow the drugs doses must be individualised with most updated weight/age. Nevertheless paediatric pharmacokinetic is not the only challenge in CF but pharmaceutical forms, adherence, as well as clarity of prescriptions and parents also play a big part of it. Current experience in the wards and clinics suggests that there is area for improvement in the way of prescribing.

1.3. Cystic Fibrosis- Disease and epidemiology.

CF is an autosomal recessive genetic disease affecting upper and lower airway, lungs, exocrine pancreas, small and large intestines, hepatobiliary system, salivary and sweat glands, and vas deferens[16,17]. It is also known as muscoviscidosis disease or fibrocystic disease of the pancreas.

CF is the most common inherited, autosomal recessive disorder in Caucasians, with a prevalence of approximately 1 in 2500 live births[18]. The

underlying abnormality lies in the chloride ion channel encoded by the cystic fibrosis transmembrane conductance (CFTR) gene[19]. CFTR is a large glycoprotein and a member of the adenosine triphosphate (ATP)-binding cassette superfamily of proteins. CFTR is expressed in many cell types, with phenotypic alterations primarily identified in epithelial cells of airways, sinuses, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system. Dysfunction of CFTR leads to a wide and variable array of presenting manifestations and complications[20].

Although technically a rare disease, CF is ranked as one of the most widespread life-shortening genetic diseases.

In 1997, about 1 in 3,300 Caucasian children in the United States was born with cystic fibrosis. In contrast, only 1 in 15,000 African American children suffered from cystic fibrosis, and in Asian Americans the rate was even lower at 1 in 32,000[21]. At present over 100,000 people suffer from this disease worldwide[22].

It is most common among nations in the Western world. Approximately 1 in 25 people of European descent, and one in 30 of Caucasian Americans[23] is a carrier of a cystic fibrosis mutation. Although CF is less common in these groups, approximately 1 in 46 Hispanics, 1 in 65 Africans and 1 in 90 Asians carry at least one abnormal CFTR gene[24,25]. An exception in Europe is Finland, where only one in 80 people carry a CF mutation[26].

During the past two decades, care for European patients with CF has been increasingly organized in specialized centres and diagnoses generally

reported to regional or national registries. This facilitates determination of the prevalence of CF for most European countries.

A recent study tried to find the EU prevalence and the results still vary depending of countries. Table 1.1 shows the prevalence in most of the 27 EU members. In this study, the calculated prevalence value is 1.37 per 10,000 in the UK and in Spain 0.5 per 10,000[27], which is well below the requirement of less than 5 per 10,000 for orphan designation in the EU[28].

Most recent data in the UK shows that around 10,500 people in the UK have CF, one in every 2,500 babies born[29]. More than half of the cystic fibrosis population in the UK will live past 41, and improved care and treatments mean that a baby born today is expected to live even longer. The prognosis of cystic fibrosis has improved substantially so that now more than half of the patient population is in the adult age range[30].

Whilst previously, CF was a disease for paediatrics only, north American data from Cystic Fibrosis Foundation Patient Registry Annual Data Report inform that the median predicted survival age for patients has increased from 25 years in 1985 to 37 years in 2008 and 39.3 in 2014 (this means that 50 percent of individuals with CF in the Registry in 2014 are expected to live to 39.3 years of age)[31]. Although research might seem controversial to American data, UK research showed that patients born today are expected to have a median survival into their sixth decade[32], the real fact is that the age survival is *in crescendo*. According to United Kingdom CF Registry 2010 the median survival for patients with cystic fibrosis is

currently 41.4 years. However, the median age at death is currently 27 years. Most people with CF who die each year are young adults.

Severely ill patients may need lung, heart or heart/lung transplants. Annual expenditure on standard care (excluding transplantation) for cystic fibrosis in England is around £100m[33].

Children with CF born after year 2000 can be expected to survive well into their 50's[34]. The usual cause of death is respiratory failure. The increased life expectancy of CF patients is a challenge to paediatric teams unused to managing medical problems unique to adolescents and young adults[35].

Table 1.1. Population and prevalence of patients with CF in EU countries[27]

Country	CF prevalence (per 10000)	Estimated CF incidence
Austria	0.839	1:3500
Belgium	1.03	1:2850
Bulgaria	0.226	1:2500
Cyprus	0.335	1:7914
Czech Republic	0.55	1:2833
Denmark	0.761	1:4700
Estonia	0.618	1:4500
Finland	0.123	1:25000
France	0.750	1:4700
Germany	0.829	1:3300
Greece	0.521	1:3500
Ireland	2.98	1:1353
Italy	0.872	1:4238
Netherlands	0.781	1:4750
Poland	0.256	1:5000
Portugal	0.271	1:6000
Romania	0.106	1:2056
Slovakia	0.627	1:1800
Slovenia	0.328	1:3000
Spain	0.546	1:3750
Sweden	0.403	1:5600
United Kingdom	1.37	1:2381

1.4. Cystic Fibrosis- Diagnostic

Since October 2007, newborn screening for CF has been in place throughout the UK; the majority of new diagnoses are via it. Conventional methods of diagnosis are still used however to either confirm the screening results or for the children born before the introduction of neonatal screening tests and patients coming from abroad.

1.4.1. Newborn screening in the United Kingdom.

The first test is the heel prick test. Immunoreactive trypsinogen (IRT) is measured on a dried blood spot obtained on the Guthrie card during the first 7 days of life. Samples with abnormally raised IRT levels will undergo CFTR mutation screening as per the chart in Figure 1.1.

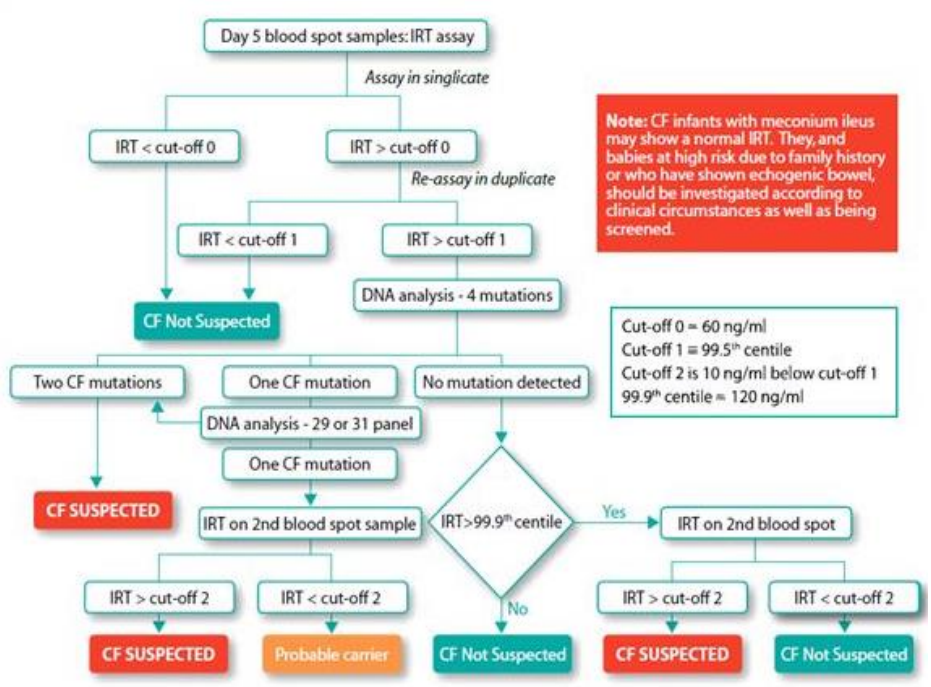


Figure 1.1. National standard screening process for newborn screening for CF (2014)[36]

If the screening result comes back positive, further tests are needed[37]. A Clinical CF Nurse Specialist (CNS) will contact the family normally within the first week of the positive result. A mandatory sweat test to confirm a positive result of the genetic test must be performed. It is a very stressful time for parents and the CF Team in the UK works within a group of experts to provide the most instructive information in a delicate way.

It is hard for parents to accept this diagnose as CF babies are normally well and treatment does not commence at this time, except of pancreatic enzyme supplements if symptoms show possible pancreatic insufficiency. Before this is actioned, a stool sample to identify elastase is performed.

The child's primary care doctor is informed and an appointment in CF outpatients' clinic is arranged for the parents within a week after the diagnosis and then they meet each member of the multidisciplinary team: consultant, CNS, dietician, physiotherapist, pharmacist and clinical psychologist. Home visits are organised with an aim to educate parents in their understanding of CF disease. The CNS specialist has a crucial role in being the parents' point of contact for any CF related problems. If proven that the baby is pancreatic insufficient, medication with pancreatinin enzymes is started straight away and depending on the parents and how ready they feel they can commence a new treatment, then fat soluble vitamins or/and prophylactic antibiotics are commenced.

1.4.2. Sweat test.

Sweat test measures the amount of Chloride in the sweat and its testing will reliably make the diagnosis in 98% of patients[38]. Despite the availability of genotyping (and because of its limitations) the majority of children in whom CF needs to be excluded will undergo sweat testing. This group will include the following:

A. Child with suggestive history / symptoms/ examination.

B. Sibling of a known case (even if asymptomatic).

C. More distant relative of known case if clinical suspicion.

Results must be interpreted in the clinical context[39]

- Normal range Cl^- <30 mmol/l.

- Boarderline Cl^- 30 to 60 mmol/l.
- CF confirmed Cl^- >60 mmol/l.

Chloride is the primary ion measured; sodium should not be measured alone. The diagnosis of CF should be made on the basis of two sweat test results, not one, to confirm that no false negative or positive results have occurred.

False negative results. Cases are increasingly recognised where the clinical picture of CF is supported by genotyping excluding the diagnosis on the basis of a normal sweat test alone. It is then recommended to perform a genetic test.

False positive results. Those which may be encountered include malnutrition or skin disorders such as severe dermatitis/eczema. Transient increases in sweat electrolytes have also been reported in young patients with immunodeficiency states[38].

1.4.3. Clinical presentation symptoms.

Thanks to the newborn screening, the clinical presentation of one or two decades ago has become rarer. As mentioned in point 1.4, the exceptions are children born before the screening technique was available as these children may present late with clinical features, and also children born in countries with no neonatal screening. Lack of experience of clinical staff may lead to further delays in diagnosis in such groups of children. The history and/or examination will usually raise suspicions of the CF diagnosis. Common features are:

- recurrent respiratory infections,
- failure to thrive with steatorrhoea,
- finger clubbing and/or
- nasal polyps.

Other features in a baby that mean CF must be excluded include:

- meconium ileus,
- rectal prolapse,
- salty tasting skin,
- prolonged obstructive jaundice,
- electrolyte disturbance suggestive of Pseudo-Bartter's syndrome and unexplained haemolytic anaemia,
- hypoalbuminaemia and/or
- oedema.

1.4.4. Genetic analysis.

There are nearly two thousand identified mutations in the CFTR gene, although not all of them are definitely associated with the clinical presentation of CF. There is a special genetic mutation nomenclature. The most common mutation in the Caucasian population is a class II mutation, F508del = new nomenclature (protein): p.Phe508del = new nomenclature (nucleotide) c.1521_1523delCTT[40].

Any child diagnosed with CF will have a genetic test in order to facilitate screening for other family members. Mothers giving birth to a CF child are also genetically tested to allow prenatal diagnosis of future pregnancies.

Genetic therapy is currently in study. Hence all CF patients are genotyped. Also, in newborn siblings of affected children, cord blood should be taken at the time of birth.

Pancreatic status should be confirmed with a faecal elastase in all cases.

1.4.5. Other tests.

To support the diagnosis of CF, the following tests can also be performed:

Stool elastase[38]: low in CF with pancreatic insufficiency (usually <15 mcg/g). Normal levels (are expected by day 3 in term infants and by 2 weeks of age in those born less than 28 weeks gestation, so tests should not be performed before this time.

- Normal > 200 mcg/g stool
- Moderate pancreatic insufficiency 100-200 mcg/g stool
- Severe pancreatic insufficiency < 100 mcg/g stool

Nasal potential difference (PD)[38]: it is recommended to do it once all other CF investigations are done only if there is still doubt of the diagnosis as it is a difficult investigation. It is also difficult in small children as requires co-operation, but may be useful in older indeterminate cases (over 8-10 years). If a child is going to have a procedure under general anaesthetic, then this is the best time to perform it. Doctors rarely obtain useful readings in the presence of nasal polyps or if there has been previous nasal surgery and the technic should be postponed if the child has had a recent cold.

1.5. Cystic Fibrosis-Pharmacological treatments.

Despite great advances in supportive care and in our understanding of its pathophysiology, there is still no cure for the disease but many treatments are available to manage it, including physiotherapy, nutrition and obviously pharmacotherapy[41]. Some reviews highlight salient insights into pathophysiology and candidate molecules suitable for CFTR pharmacotherapy. But no reviews have been found to analyse the quality of prescribing in CF patients.

Pharmacotherapy is key to help patients keep the disease controlled. However, due to associate pathologies of CF, the number of medicines CF patients take is expected to be rather large. Table 1.2 summarises the main therapeutic groups of drugs used in CF.

The pharmacological management of patients with cystic fibrosis largely focuses on maintaining lung function; however, other aspects of care, such as managing pancreatic insufficiency, are also important[42], especially in young children whose growth is affected due to poor absorption of nutrients and having a negative effect on the progression of the disease.

Table 1.2. Main pharmacological therapeutic groups of drugs used in CF.

Main treatment by body-system	Sub therapeutic group
• Anti-infectives	• Anti bacterials, antifungals
• Endocrine system	• CF related Diabetes
• Gastro-intestinal	• Antacids, proton pump inhibitors, prokinetics, laxatives
• Nutrition and metabolic disorders	• Electrolytes, metabolic disorders, vitamins
• Respiratory	• Glucocorticoids, Ivacaftor, mucolytics, bronchodilators

Managing the respiratory symptoms and complications of CF forms the backbone of treatment. Nebulised, oral and intravenous antibiotics are used to prevent bacterial colonisation and treat infection. Other treatments include antifungals, mucolytics and physiotherapy[42]. Treatments for the non-respiratory manifestations of CF include enzyme supplements; anti-reflux or prokinetic medication; proton pump inhibitors; insulin for pancreatic insufficiency; ursodeoxycholic acid for liver dysfunction; laxatives for constipation as well as systemic acetylcysteine to avoid bowel obstruction often named DIOS (Distal Intestinal Obstruction System).

Vitamins and supplements like calcium for the bones or sodium to replace the loss of salt in the body are also part of key medication that is likely to be life long or at least modified during seasons or countries where CF patients live.

1.5.1. Respiratory system.

Respiratory care is extremely important in CF children. Lung function can deteriorate fast, with challenges to reverse to previous spirometry.

A. Mucolytics

Most common mucolytics used in CF are delivered by nebulisation with the aim of clearing mucociliary in the lungs.

- Hypertonic Saline

Hypertonic saline (HTS) nebules help by breaking the mucus and are used from an early age in the childhood of a CF child. Hypertonic saline can be used in the short term to induce sputum as well. They can cause bronchoconstriction[43] so the first dose should always be given with spirometry before and afterwards.

HTS is administered immediately before physiotherapy or in some cases it is combined with physiotherapy. There are different preparations in the market, the most common one is the 7% HTS but if patients are not tolerating this strengths, 3%-6% concentrations can be worked out by mixing the 7% HTS with water for injections when other strengths are not available in formularies.

Sometimes other mucolytic agents need to be introduced: recombinant DNase (Dornase alfa) or NAC (N-Acetyl cysteine) is also used for our kids in the UK as unlicensed when their mucolytic output is compromised.

- Dornase alfa (DNase)

DNase is a synthetic enzyme that cleaves neutrophil derived DNA in sputum to reduce viscosity and thus in theory to aid sputum removal by breaking it easier.

In the UK, it is licenseg for use from five years of age[44] and the Consultant decides when to start treatment with DNase although a European report initially recommended starting it in all patients that are 6 years old or older, independently of the lung function[45]**.**

DNase dose is 2.5mg in the afternoon 1 hour before physiotherapy by appropriate compressor and nebuliser i.e., standard or faster E-flow or I-Neb (if using the I-Neb 1ml DNase is nebulised and the rest is discarded).

DNase is considered a safe drug as adverse events are rare and mild.

From a finance prescribing point of view, DNase is a high cost nebuliser (over £500 per patient/month when used once a day) and medicines optimisation is required. Advice is given to children and careers as the mucolytics need to be nebulised before physiotherapy at least once a day in the evening.

- N-Acetylcysteine (NAC)

There is no nebulised NAC preparation licensed in the UK and the IV preparation is the only alternative to be used nebulised (normally diluted with WFI) due to its mucolytic action in CF children that either

do not fully respond to Dornase alpha or require further mucolytic effect with HTS or even whilst being on DNAse too.

B. CFTR Modulator: Ivacaftor.

Ivacaftor is a small molecule which binds at the cell surface and leads the chloride channel to open (this is termed 'potentiation'). It has mostly been administered twice daily at 150mg in tablet form. It is crucial that it is taken with or very shortly after a high-fat meal or snack, as otherwise absorption is poor. Tablets must not be chewed. Recently EMA approved a license for a form of granules that can be mixed with food.

In December 2012, Ivacaftor was approved by NHS England for clinical use in CF patients of 6 years of age and above with at least one copy of the G551D mutation. Few studies show the safety of Ivacaftor in children over 2 years old and CF organisations have requested the National Institute of Clinical Evidence (NICE) to review the licensed age from 2 years old instead of from 6 years old. The Scottish health system has approved its use in children from 2 years old with the G551D mutation.

The cost of one patient being on Ivacaftor is £14000 per 56 tablet pack, equivalent to one month's treatment (price from BNFc 2016).

Due to the very high cost of the drug, the British Commissioners in England have mandated monitoring and have imposed stopping

criteria[46] and there is no need to say that this treatment needs optimisation as well, from a pharmacoeconomic perspective.

In December 2016 NHS-England approved its commissioning for all children aged 2-5 years old with CF and at least one of nine gene mutations, after providing evidence of cost effectiveness in children aged 2-5 years old with CF with specific mutations and being this prescribed by specialist centres.[47]

Side effects like rashes or rising liver function tests were observed in some patients. If this occurs monitoring and dose reduction for patients with significant hepatic or renal impairment is recommended.

Ivacaftor presents some significant interactions, most importantly:

Azole antibiotics: (itraconazole, voriconazole) lead to inhibition of the breakdown pathways of ivacaftor and accumulation of the drug. If co-administration is necessary the dose of ivacaftor should be reduced; manufacturers suggest to twice weekly although this comes from modelled data, not human PK studies, and anecdotally, this may lead to loss of efficacy. Consultant advice should be sought in this event. Ivacaftor levels are not currently available, but sweat Cl^- could provide a useful surrogate for bioavailability.

Clarithromycin: also leads to accumulation of the drug so suggested take ivacaftor three times a week. There is no interaction with azithromycin.

Rifampicin: will significantly reduce ivacaftor levels; co-administration not recommended.

High dose corticosteroids: may significantly decrease serum levels of ivacaftor and reduce efficacy.

c. Treatment of infection, prophylaxis and use of antibiotics (oral, intravenous, nebulised).

Table 1.3 describes most common chest exacerbation indicators[38]. The threshold of antibiotics prescribing in CF is lower than other pathologies; hence if any of the indicators show symptomatology of chest exacerbation, antibiotics are started.

Furthermore, longer courses and higher doses of antibiotics are used in the CF population than would be prescribed for other patients because CF patients have altered pharmacokinetics, with increased clearance and volume of distribution. They also require high plasma concentrations of drugs to be achieved, to penetrate viscous mucus[48].

Table 1.3. Chest exacerbation indicators.

Main chest exacerbation indicators of infection
• Increased cough, and in particular a new or increased 'wet' cough should always be taken seriously. • Adverse changes in sputum production (volume, colour, consistency). • Haemoptysis. • Increased dyspnoea. • Chest pain or tightness. • Malaise, fatigue and lethargy. • Fever > 38ºC. Although most CF chest exacerbations are not accompanied by fever. • Loss of appetite or weight loss. • Drop in FEV_1 or FVC >10% from previous recording.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

When a patient presents with an exacerbation, antibiotics are initially given orally and CNS monitors the clinical status of the child whilst feeding back to the consultants. If there is poor response after oral intake of antibiotics, IV treatment is essential.

At least two intravenous antibiotics should be prescribed to reduce the risk of antibiotic resistance which has been associated with monotherapy[49].

A combination of betalactam antibiotics with aminoglycosides has been shown to be synergistic. Ceftazidime and Tobramycin are in the United Kingdom' the first line treatment in most CF referral centres. The doses given are higher than other respiratory conditions and as per protocol, the monitoring for Tobramycin levels is performed in the hospital regularly. There is a monitoring form designed by pharmacy and used by nursing staff for aminoglycosides, this form needs to be followed and filled in prior to administering the drugs in order to comply with safety aspects of the drugs. This way it is ensured that the dose of the aminoglycoside, pharmacokinetic levels and other aspects are double checked and the risk of an administration error is mitigated.

Persistent infection and resultant colonisation produces thick mucus and causes chronic inflammation, leading to irreversible bronchiectasis (abnormal and permanent dilation of bronchus). The most common pathogens in CF are summarised in Table 1.4[50].

CF children are taught at an early age to routinely give sputum samples, which are then cultured and the sensitivities tested. This gives a recent microbiological profile against which antibiotics can be selected. Sputum induction is sometimes necessary in non-producers who are clinically deteriorating on blind therapy and this can be achieved by nebulising a hypertonic saline solution in a controlled environment. In small children and ones that cannot expectorate the usual sample used is a cough swab.

In order to prevent infections caused by *Staphylococcus aureus* (mainly in infancy), *Haemophilus influenzae* and *Pseudomonas aeruginosa* being the major pathogen in older children and adults[51], antibiotic prophylaxis can be started. Nebulised antibiotics are prescribed for patients who are chronically colonised with *Pseudomonas aeruginosa*. There are not many nebulised antibiotics in the market. However those that are, have shown to reduce the rate of respiratory function deterioration and to reduce the number of courses of intravenous antibiotics needed to treat exacerbations[52].

Antibiotics most commonly administered by nebulisation are colistin and aminoglycosides (normally tobramycin or gentamicin, but amikacin is also used, depending on sensitivities). In the UK, colistin is generally used first line and tobramycin is reserved for patients who cannot tolerate it or continue to decline despite its use. As there is no nebulised licensed preparation of any other aminoglycosides other than Tobramycin nebules, intravenous preparations must be used as

nebulised, a clear unlicensed use. As IV preservatives might cause bronchospasm, it is imperative that pharmacists screening these types of prescriptions are aware that preservative free formulation should be dispensed[53].

Table 1.4. Most common pathogens isolated in CF.

Pathogen	General Comments
Staphylococcus aureus (*S aureus*)	In the UK, flucloxacillin is recommended for long-term prophylaxis in infants under the age of two years[54]. Shown to reduce the incidence of S. aureus infection, clinical symptoms and the need for additional antibiotics[55], but its benefits are controversial as some countries recommend flucloxacillin in their guidelines against in others[56]. If prophylaxis is given, review after the child is 3 years old.
Haemophilus influenza (*H influenza*)	If the child keeps isolating influenza, UK Consultants will discuss the possibility to start long term prophylactic antibiotics. Azithromycin is the third generation macrolide in the market. The pharmacology of Azithromycin is not only antimicrobial but also has an anti-inflammatory effect that is of benefit in respiratory patients[57]. It is a well-tolerated drug amongst most CF patients despite medics using it in caution in liver function abnormalities. If this is started in patients that already are on prophylactic flucloxacillin, it should be recommended flucloxacillin to stop.
Pseudomonas aeruginosa (*P. aeruginosa*)	Chronic colonisation with the organism is associated with a more rapid decline in lung function and deterioration in chest X–rays[58]. When patients are colonised, nebulised antibiotics are prescribed. If the child's lung function deteriorates a routine admission to hospital every 3-4 months for IV antibiotics is programmed and the focus of this study is in hospitalised patients.

Aspergillus fumigatus and allergic bronchopulmonary aspergillosis (ABPA)	The mainstay of treatment for ABPA is antifungal drugs and oral corticosteroids in order to attenuate inflammatory and immunological responses[59]. Prednisolone is used for one to two weeks then taper based on clinical response. The non-enteric coated preparation prednisolone should be used in patients with CF since there are case reports of treatment failure with the enteric coated preparation[60]. A possible reason for this is that enteric coated prednisolone, is released at a pH of 6.8 and it may not be absorbed in the jejunum of CF patients where the pH is often lower than 5 for prolonged periods[61].

Since April 2015 in the United Kingdom high cost nebulisers (HCN) are considered specialised treatment for CF patients and are also commissioned by NHS-England[62], hence reference centres in secondary care have been forced to repatriate each CF patient's prescribing on HCN and their monitoring[63]. This is for some parents/carers difficult to understand and creates confusion with primary care doctors who might not be aware of the commissioning, creating potential extra costing and treatment delay. One of the quality indicators that will be observed in this study is whether primary care still keeps high cost nebulisers as part of the patient's repeat prescription. If this is the case, there is a risk of misuse and uncontrolled expenditure.

Nebulised antibiotics should be administered after chest physiotherapy and bronchodilators to maximise deposition in the lung. The importance of good labelling, dispensing and counselling is a key factor for adherence, as well as the time to nebulise these

antibiotics. The patient's daily routine is frequently discussed to best fit the regime with the child's day.

D. Pharmacology of antifungals used in CF with ABPA.

The criteria for diagnosing ABPA is challenging and the clinical diagnosis needs to be done by investigations as the clinical presentations are not specific.

Although most of the time steroids are used, antifungal therapy is also needed. Internet and media might create confusion on the use of steroids and patients are likely not to adhere to treatment even if good counselling has been provided. It is very important that the counselling the pharmacist provides is in concordance with the treatment the medics have chosen, length of steroids, and options to treat ABPA as part of optimisation and enforcement to patient's adherence as often parents have other questions and consistency should be provided.

Interactions with the co-medication have to be considered when treating ABPA. A small number of antifungal pharmacokinetic studies indicate a high inter-subject variability for itraconazole, voriconazole and posaconazole, and therefore therapeutic drug monitoring is recommended[64].

Due to the need of antifungal drugs and their pharmacology individualisation of therapy is required in paediatric population with ABPA.

After efforts from doctors deciding best treatment for the child, the prescription is the next step to confirm that treatment will be administered and the labelling precedent should be clear.

Table 1.5 covers some pharmacological aspects of main antifungals used in CF with a focus on azoles systemic therapy. Liposomal amphotericin can also be used with a local effect at the site of the infection nebulised. In summary, the treatment's options in ABPA are limited and bring several discussions to the multidisciplinary team.

Table 1.5. Pharmacological aspects of main antifungals used in CF patients with ABPA.

Drugs in ABPA	Main pharmacokinetics
Steroids	IV Methylprednisolone is used as pulse therapy every 2-4 weeks to help adherence. Oral prednisolone's absorption is pH-dependent and can be optimised using non-enteric coated preparation. See Table 1.4.
Itraconazole	Antifungal and anti-inflammatory effect, allowing lower doses of steroids to be used[65,66]. Highly lipophilic and only ionised at low pH. The absolute availability of capsules in healthy volunteers under fasting conditions is about 55% and is increased after a meal[67]. Absorption is pH-dependent and can be optimised by dividing the daily dose in two and administering the treatment only before food with an acidic drink such as cola or orange juice[68]. 99.8% bound to human plasma proteins and its apparent volume of distribution is about 11 L/kg. Half-life of itraconazole is about 24 hours. Dose-dependent pharmacokinetic behaviour[67] No routinely PK levels done. Some hospitals eg The Royal Brompton Hospital are doing trough sample levels on day 14 (in 1ml of serum into clotted blood vacutainers) with aimed level of 1 - 4mg/l.

	Current hospital practice at Barts Health NHS suggests that CF patients do not achieve therapeutic levels and this might be due to impaired absorption.
Voriconazole	Treat refractory Aspergillus spp infections and like Itraconazole reaching therapeutic levels might be a challenge too[69]. However voriconazole may have an advantage over itraconazole because it has a 96 per cent oral bioavailability[70] and is less protein bind to albumin (around 58%). Due to photo sensibility of voriconazole, albumin levels can be considered in countries/seasons where sun exposure is frequent. Linear non-saturable dose-exposure pharmacokinetic profile has been described for children[71] In order to obtain efficacious blood levels, daily doses of up to 14 mg/kg are needed in the paediatric setting (compared with 6 to 8 mg/kg for adults). However, blood concentration variability and sub-therapeutic values in the paediatric population have also been reported[72]. Little literature is available in regards sample PK levels, however The Royal Brompton Hospital take trough sample levels on day 3 (in a 1ml of serum into clotted blood vacutainers) with aim levels of 1.3 - 5.7mg/L, and this can be used as a reference guide.
Posaconazole	This is the most recently approved triazole antifungal[73] and has a long elimination half-life (>24 h). A number of factors have been demonstrated to impact upon posaconazole absorption including food (and fat specifically), gastric pH (and the use of proton pump inhibitors), mucosal health, and frequency of administration (due to saturable absorption)[74]. Clinical pharmacokinetic studies in non-CF patients have shown that the co-administration of posaconazole with a nutritional supplement containing 14g of fat increases the AUC by more than 200%[75]. Limited clinical pharmacokinetic and pharmacodynamic data are available. It is highly protein bound (> 98 %)[76] and there is limited date in children[77]

Allergies

Repeated courses of high-dose antibiotics put patients at risk of developing allergies to antibiotics at any time during a course of antibiotics. The reactions can manifest as bronchoconstriction or rash and further exposure could escalate to anaphylaxis. All allergies and their nature should be carefully documented in patients' notes. This will help to identify patients who may be suitable for desensitising (administering increasing concentrations of an antibiotic by infusion to a patient until the therapeutic dose is achieved), should this be necessary due to multiple resistance problems.

1.5.2. Gastrointestinal system and nutritional care.

The incidence of gastro-oesophageal reflux disease (GORD) is increased in CF patients and this is possibly due to hyper-acidity of gastric secretions, constipation and increased abdominal pressure secondary to coughing. Uncontrolled GORD aggravates CF disease[78].

Motility stimulants are frequently used, being the most common domperidone and erythromycin. Doctors have to evaluate individually if the risk of cardiac effects outweighs the beneficial use of domperidone[79].

H2-antagonists or proton pump inhibitors (PPIs) are prescribed to reduce the acidity of secretions. These may also improve the effects of pancreatic enzyme supplements in preventing fat malabsorption.

The licensed Ranitidine liquid is formulated with ethanol and the tablets present as effervescent or normal tablets. When, for religious reasons

primary care prescribe unlicensed Ranitidine liquid (so no alcohol is added), the strength varies depending on the manufacturer. This poses a risk of misdosage for the patient as some parents remember the dose primarily by volume.

Omeprazole and Lansoprazole are the most common PPIs used and the presentations also vary, hence the importance of having this written in the prescription.

Pancreatic insufficiency is another concomitant disease to CF, is prevalent in young infants with CF and has a significant impact on growth and nutrition[80]. Some infants may initially be pancreatic sufficient however they may become insufficient over time, this must be considered should they present with symptoms of fat malabsorption or poor weight gain.

Pancreas failure and inability to secrete digestive enzymes leads to malabsorption of fats and fat-soluble vitamins as well as some proteins and carbohydrates. In these patients, it is essential to supplement meals and snacks containing fat with pancreatic enzymes. The amount of enzyme required is determined on an individual basis based on the fat content of food consumed.

There are several enzymes available on prescription but the most commonly used brand in CF is called Creon®. Creon® contains three digestive enzymes - lipase, protease and amylase, helping digest the different component of foods: fat, protein and carbohydrates respectively. The enzymes come in various strengths including enteric-coated microspheres (Creon® Micro), and capsule forms.

Enzyme capsules should be swallowed whole and are generally taken at the start of a meal, however enzymes can be taken at the beginning, during, or at the end of a meal.

The enzymes are most effective for 20-30 minutes so ideally meals should be finished within this time. This might not be practical for all children so additional enzymes may be given towards the end of a meal or between the main course and the pudding.

It is important to have quick and easy access to enzymes to aid adherence. Between the ages of 2-5 years old children should be encouraged to learn to swallow capsules whole. Capsules can still be opened out and taken with fruit puree or yoghurt but this may compromise their effectiveness, and can be less convenient, especially as a child gets older.

Pancreatic enzymes should be taken with all meals, snacks and drinks containing fat. Education on the amount of Creon® taken with different foods is provided by the dietitian.

Dietitians play an important role in educating patients and parents of children to tailor enzyme use to the needs of the individual. Over-use of enzymes can present with the same symptoms as malabsorption.

Each patient has a preference pancreatic medication and we must respect this in order to help adherence, hence a CF pharmacist would expect a pancreatinin prescription to be prescribed branded.

Another common gastrointestinal presentation in CF children is constipation with a complication known as distal intestinal obstructive

syndrome (DIOS) and this occurs most frequently in pancreatic-insufficient patients as a result of accumulating of partially digested food. It is important good pharmaceutical care as well as outstanding prescribing practice, so children and carers use the medication in the best possible way.

Furthermore, salt depletion in CF patients tends to occur during hot weather because of increased sodium and chloride loss in sweat. During summer months, some patients may require sodium supplements, such as slow sodium 600mg tablets or unlicensed sodium capsules or oral solutions. Dioralyte® sachets are also used as they are more palatable to younger children.

Another gastrointestinal system that must be mentioned here in CF patients is the liver disease which causes hepatomegaly with significantly elevated liver function tests, abnormal clotting or evidence of cirrhotic changes on liver ultrasound scan (USS).

These children with CF liver related pathologies are treated with vitamin K supplement but as the impaired liver will create biliary stasis, patients will also be treated with ursodeoxycholic acid to promote bile flow and also displace toxic endogenous bile acids which accumulate in cirrhotic livers. A review from the Cochrane Library concluded that there was insufficient evidence to support the routine use of ursodeoxycholic acid in CF[81]. However there is some evidence supporting its use to improve cholestasis in patients with liver abnormalities[82].

Aspirin and NSAIDs in those with documented cirrhosis should be avoided and drugs to be used in caution with liver disease include: fusidic acid, minocycline, rifampicin, and azithromycin, itraconazole and voriconazole.

1.5.3. CF-related Diabetes

CF-related diabetes (CFRD) rarely occurs in patients under 10 years old although up to a third of this age group will already have impaired glucose tolerance and it is mainly managed with insulin.

All CF individuals with exocrine pancreatic insufficiency have insulin deficiency, which worsens with increasing age. Insulin secretion is reduced even in individuals with normal glucose tolerance. There is an increase in the prevalence of impaired glucose tolerance and diabetes with age. The reported prevalence of CFRD depends on the diagnostic criteria used and screening methods, but approximately 50% of CF patients will have CFRD by age 30. CFRD is distinct from either type 1 or type II diabetes mellitus and there are different approaches to diagnosis and management.

Current CF trust recommend screening for abnormal glucose tolerance and diabetes in all CF patients over 12 years.

The primary cause of the abnormal glucose tolerance in CF patients is insulin deficiency so the treatment for this is insulin. Insulin has been shown to improve lung function and nutritional status in CF patients. Oral hypoglycaemic agents are not used in CF patients.

Treatment starts in every patient with a diagnostic of diabetes or with symptomatic hyperglycaemia. CF trust has diagnostic criteria for CF related diabetes. Some patients are considered for treatment without clear diagnosis of diabetes if they have a declining lung function or nutritional status with no other cause found or nutritional concerns, for example on overnight feeds or supplements and not gaining weight.

The endocrine department is heavily involved and they decide the type of insulin to prescribe. Paediatric endocrinology teams in University hospitals have a comprehensive guideline on insulin types, starting doses and the use of higher doses in children already receiving high doses of steroids.

The safer insulin prescribing guidance published in January 2017 by National Institute for Health and Clinical Excellence (NICE) recommends that all health care professionals prescribing, screening or administering insulin should have had training in the safe use of insulin. The reason for this is that there are many clinical incidents in the UK each year related to incorrect insulin prescription and administration. Common incidents include giving the wrong insulin, lack of clarity in prescriptions, and drawing up or giving insulin with the wrong type of syringe.

Safe insulin prescriptions[38,83]

- Get the correct insulin name (there are some insulins with similar names) but also the presentation, e.g. cartridges, disposable pen.

- State when the insulin is to be given. For short acting insulin this will be before a meal and not at a particular time of day.
- If the dose is variable (for example short acting insulin for meals) you must make it clear how the dose will be decided.
- For paper prescriptions the word “units” must be written in full and never “u” or ”iu”. A badly written “u” can be mistaken as a zero.

1.6. Hospital Pharmacists in the UK.

The United Kingdom’s hospital pharmacists (HPs) are seen as the experts of the drugs: pharmacokinetics and pharmacodynamics conversations with other healthcare professionals occur as part of daily routine work during ward visits. HPs are required to be a great source of advice for patients and work closely with medical and nursing staff on the wards to ensure that the most appropriate treatment is being prescribed safely.

Hospital pharmacist inform patients on all aspects of their medicines, including recommending choices, as well as administration routes and dosages, which are all very dependent on the individual's needs.

Medics rely on HPs to recommend safe combinations of medicines or solutions to specific patient problems. HPs also inform them of any potential side effects and check that medicines are compatible with existing medication as well as monitor the effects of treatments

prescribed to ensure that they are providing effective, safe and appropriate treatment to the patient.

Nursing staff also rely on HP to provide a clinical screen, counsel on administration and supply the right pharmaceutical form for each patient.

A HP undertakes series of training in order to develop to a specialization. Table 1.6 shows mains tasks of HPs according to their seniority. The complexity of each task varies depending on the seniority of the HP.

Grades are set up from band 5 for pre-registration pharmacists (in the UK last year students that choose to do their placement in a hospital, follow structured interviews to mark them). The students that passed these competitive interviews for hospital pharmacy are offered a year student place (remunerated) in order to taste what a hospital pharmacy career is like as well as helping prepare them for the final exam.

At the end of the pre-registration year, the student sits the final exams of their degree and once passed they can register in the General Pharmaceutical Council, which is mandatory for work as a pharmacist (community, industry, prison, hospital).

Once registered, the pharmacist can apply for band 6 jobs through highly selective and competitive interviews.

Table 1.6 Main tasks delivered by HP depending on seniority.

Band	Ward cover	Ward rounds	Financial	Organizational	Educational
6	✓				
7	✓	✓			✓
8a	✓	✓	✓	✓	✓
8b		✓ (clinics)	✓	✓	✓
8c			✓	✓	
9	Chief pharmacist				

1.6.1. Band 6 pharmacist: Rotational Pharmacist.

Successful pharmacists will start their careers with a rotational plan together with an extensive educational programme. This programme is followed by the junior pharmacist (also known as foundation pharmacist) and looked after by his/her designated Educational Supervisor, normally a highly specialist pharmacist (from band 8a upwards).

The programme for a band 6 pharmacist is supported by the Clinical Diploma training, which focusses on at two sets of 18 months each. Each set is also divided into three six months programmes with a clear focus on different areas, from clinical, governance, audit, finance, manufacturing, purchasing, dispensing, etc.

During the six month period of each learning programme the foundation pharmacist will have regular meetings with their Educational Supervisor to ensure they are developing in the required way within clinical pharmacy. At the end of 18 months set, the Diploma student will meet with a panel of expert pharmacists to assess student's level of knowledge

and they will decide if the student should repeat the same learning set or whether the pharmacist can carry on to the next step of her/his Diploma.

After the end of the Diploma the pharmacist will be ready to start focussing on specific clinical areas they would like to join in, and often either they apply for band 7 jobs or stay as band 6 for a certain time.

Generally speaking, band 6 pharmacist stay in this rotational post between 3 to 6 years; senior pharmacist encourage them to make sure what speciality they want to focus on.

One of the minimum requirements to apply for band 7 jobs or to be selected to Band 7 interviews at Barts Health NHS is the possession of the Clinical Diploma but a Band 7 pharmacist also needs to show in the interview good level of clinical knowledge for the area they apply.

1.6.2. Band 7 pharmacist: Specialist Clinical Pharmacist.

This section focusses on Women and Children Specialist but Band 7 pharmacists can be rotational and are also part of departments such as renal, hepatology, neurology, surgical, intensive care, production, oncology, commissioning, gastroenterology, respiratory, care of elderly, cardiology and infection disease.

A women and children specialist clinical pharmacist (band 7) at Barts Health hospital will also follow a rotation of each speciality (depending on the type of hospital these may vary): neonatal intensive care, respiratory, trauma and surgery, neurology, gastroenterology, paediatric intensive care, obstetrics in high dependency unit, gynaecology. Being part of each

rotation is key in order to be able to understand the pharmacokinetics difference in infants, children, adolescent or obstetrics.

Band 7 pharmacists undertake higher responsibility for their area. They need to liaise with consultants, clinicians, managers, nursing staff, other clinical pharmacists, pharmacy operational managers and trust medicines effectiveness pharmacist. They must also deal with parenteral nutrition issues, supply problems, etc.

They will participate in developing clinical pharmacy services to the women and children's wards and organise the training of band 6 pharmacists, junior doctors and nursing staff too.

Band 7 pharmacists must demonstrate excellent pharmaceutical knowledge of the drugs in their area, from pharmacology, to supply in hospital or even community environment and when supply problems arise, with the aid of a senior, the band 7 pharmacist will decide the most appropriate alternatives after balancing clinical/cost benefit versus the drug that needs to be substituted.

Regulations to allow pharmacists to prescribe independently came into effect in 2006. An independent prescriber pharmacist may prescribe autonomously for any condition within their clinical competence. An intense training followed in the area to prescribe is undertaken and at our trust a senior band 7 can start this training when funding is approved.

It is expected that a band 7 pharmacist will monitor medicines use within the ward area and this includes recording of significant clinical

interventions and risk management like participating in investigating clinical incidents; recording significant clinical incidents/near misses as well as ensuring compliance with medicines legislation and local policies.

As a specialist pharmacist the band 7 HPs might be requested to participate in ward rounds, clinical meetings or out-patient clinics in order to provide pharmaceutical advice to prescribers and other health care professionals. It is not unusual to deal with primary care enquiries as more often HP get phone calls from doctors in general practitioners' surgeries.

Other roles undertaken at a band 7 level are participating in ward-based clinical audits and the development and implementation of treatment protocols and guidelines for use of medicines within the clinical area.

A band 7 pharmacist as well as a senior band 6 is asked to act as a role model and mentor for clinical pharmacy.

The above are daily tasks required for a band 7 pharmacists but they also undertake other roles that are not less important.

Generally speaking the culture of UK senior HPs aim to keep staff happy and motivated as this is essential to support learning and achieve best results for the department. Monthly communication meetings occur within the women and children department and weekly meetings for general development too. In the UK it is also common to organise team building exercises to enhance best communication within the team.

A band 7 pharmacist within the women's and children's department will have a speciality preference and might work towards a higher specialisation in the area in order to achieve the next opportunity as a band 8a, the next recognised step for a band 7 hospital pharmacist.

1.6.3. Band 8a and above.

The responsibilities and tasks are greater as high as the pharmacist progresses hierarchy. Monthly finance reports are pulled out and addressed properly to each medical budget holder and commissioning groups.

Highly specialist pharmacist or band 8a role are normally attached to a clinical area or need (for instance risk specialist) but also manage a team and report closely to 8b pharmacists who are often the budget holders for the Department.

The role referring from now on is CF highly specialist pharmacist, which is a band 8a and therefore has an in depth knowledge of tasks taken by band 7 and 6 pharmacists. Being a senior role, the CF pharmacist is expected to multitask hundreds of jobs and participates in the recruitment of junior and band 7 pharmacists, as well as support the team and the juniors. The CF pharmacist has excellent knowledge of the consensus document outlining pharmacy standards in CF care published by the CF trust in November 2011.

A highly specialist pharmacist provides a comprehensive medicines management service to children on long term conditions that relate to CF.

They work with multidisciplinary teams to enhance optimal prescribing and provide training and education for children, parents and other members of the multidisciplinary team.

The provision of professional advice is required and support to other health and social care professionals within the community health services on the safe prescribing, handling and administration of medicines is part of daily routine.

Band 8a pharmacists in CF will lead on the medicines aspects of patient care to optimise medicines as well as reduce medicine related risks and improve adherence to taking medicines. This also includes co-ordinating and leading on interventions to reduce medicine related problems by developing care plans in agreement with clinicians, patients and other health and social care professionals as well as facilitate collaborative working between multidisciplinary teams/agencies.

The developing of best practice guidelines and medicines processes fall under band 8a pharmacist responsibilities. These must be efficient, consistent, practical and sustainable within the constraints of the existing systems and take into account the values of patients and their careers.

In CF, a daily identification of areas of risk relating to medicine use in primary care is a routine task as pharmacists facilitate compliance with medicines legislation to ensure delivery of safe standards in the prescribing and handling of medicines in the community across health and social care, including schools.

Working with the CF team as well as Clinical Commissioning Groups (CCG, these are a group of prescribing experts and they hold the budget for primary care) medicines management teams and community pharmacy leads develop and implement strategies to improve medicine adherence in paediatric CF population.

Furthermore band 8a pharmacists are expected to deputise for the operational lead of the department during their absence (8b pharmacists), a big role for a pharmacist in the UK.

The input of the band 8a pharmacist in CF is of great importance because of multiple disease states and the use of polypharmacy. As the complexity of the pharmacology in CF is enormous, the pharmacist delivers better care within CF children amongst other factors. Having a CF pharmacist in the department will result in increasing the quality of the prescribing as this is expected to be at a great standard.

CF patients come into hospital and some of their regular medication is stopped during their stay. The re initiation or any possible changes done during the weeks the patients have been having IV therapy must be managed appropriately. Furthermore CF treatment also has a high-cost area of drug therapy and the pharmacist can have a significant input in medicines optimisation.

It is accepted that a child with CF might take a number of medicines that would rarely decrease whilst they grow and reach adult phase. A CF pharmacy special interest group held its first meeting in February 2000

and there it was acknowledged that treatment for CF must be individualised to fit in with a patient's lifestyle.

Also, the volume of drug therapy and other treatments, such as physiotherapy can be felt as very time consuming. Therefore planning treatments around individual patient's requirements and modifying treatment ideals are necessary in order to achieve best medicines optimisation and improve patient adherence.

1.6.4. Ward visit and drug chart.

Medicines reconciliation is an essential part during admission process of a patient. New medication prescribed might interact or have an effect with the regular medicines and is important to gain the most up to date information and the actual way the patient takes the medicines.

In the UK, the HP or a senior technician will list the name of the medicines that patients take if they have not yet been written up in the drug chart. However if the regular medication has been completed in the drug chart, the pharmacist will give a number and will link this to the front page of the drug chart with comments if needed. The comments will be used for discharge, to review the previous posology and the new one and communicate with primary care as well as with the patient, reinforcing adherence. The next serial of figures 1.2 to 1.7 are some examples of the drug chart.

The drug chart is the tool used in UK hospitals to record the medication prescribed and administered to each patient. The drug chart is an A4

booklet with different pages in it and each pages covers the following information:

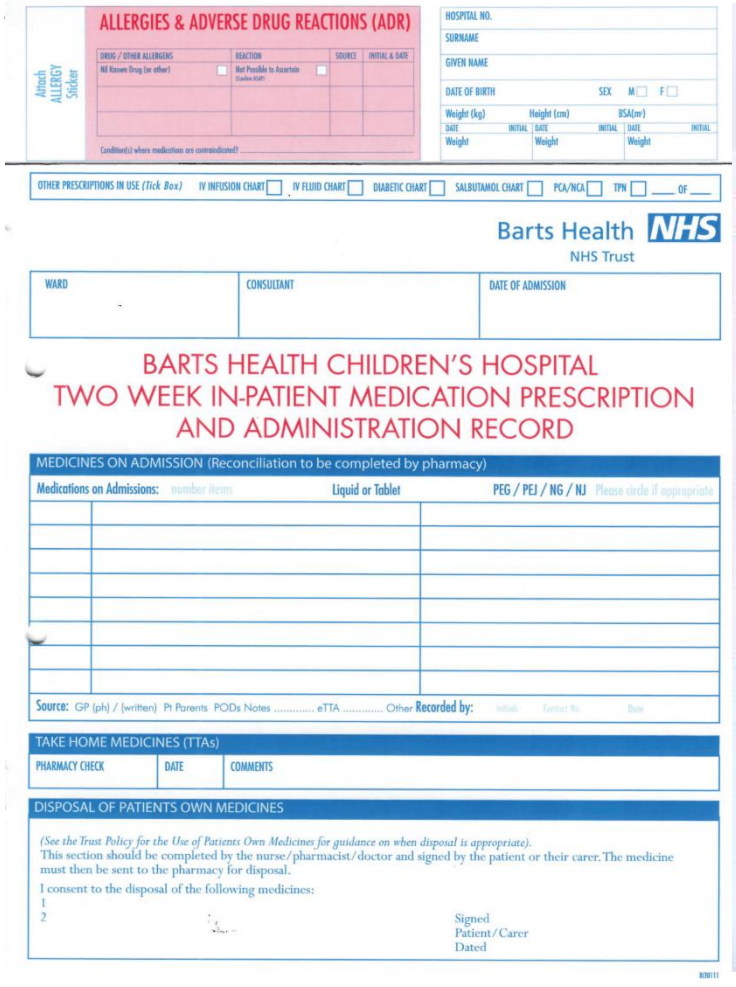
Page 1: Used for medicines reconciliation, allergies, demographic information and relevant information for pharmacy.

Page 2: Once a day, loading dosing drugs prescription and administration and drug blood levels record.

Page 3-6: Regular medication to be taken during hospital admission and administration records. And page 6 also has space to record the prescribing and requirement of oxygen/patient' saturations.

Page 7: Medication to be prescribed as when required.

Page 8 (last page): Drugs not administered code and intravenous flushes.



ALLERGIES & ADVERSE DRUG REACTIONS (ADR)

Attach ALLERGY Sticker

DRUG / OTHER ALLERGENS | REACTION | SOURCE | INITIAL & DATE

Nil Known Drug (or other) | Not Possible to Ascertain

Condition(s) where medications are contraindicated?

HOSPITAL NO.

SURNAME

GIVEN NAME

DATE OF BIRTH SEX M F

Weight (kg) Height (cm) BSA(m²)

DATE INITIAL | DATE INITIAL | DATE INITIAL

Weight | Weight | Weight

OTHER PRESCRIPTIONS IN USE *(Tick Box)* IV INFUSION CHART IV FLUID CHART DIABETIC CHART SALBUTAMOL CHART PCA/NCA TPN ___ OF ___

Barts Health NHS

NHS Trust

WARD | CONSULTANT | DATE OF ADMISSION

BARTS HEALTH CHILDREN'S HOSPITAL TWO WEEK IN-PATIENT MEDICATION PRESCRIPTION AND ADMINISTRATION RECORD

MEDICINES ON ADMISSION (Reconciliation to be completed by pharmacy)

Medications on Admissions: number items | Liquid or Tablet | PEG / PEJ / NG / NJ Please circle if appropriate

Source: GP (ph) / (written) Pt Parents PODs Notes ..... eTTA ..... Other Recorded by: Initials Contact No. Date

TAKE HOME MEDICINES (TTAs)

PHARMACY CHECK | DATE | COMMENTS

DISPOSAL OF PATIENTS OWN MEDICINES

(See the Trust Policy for the Use of Patients Own Medicines for guidance on when disposal is appropriate).
This section should be completed by the nurse/pharmacist/doctor and signed by the patient or their carer. The medicine must then be sent to the pharmacy for disposal.

I consent to the disposal of the following medicines:

1

2

Signed
Patient/Carer
Dated

B20111

Figure 1.2. Front page of drug chart: medicines reconciliation. The allergy and demographic part is an A4 size and will be seen after each turn of page in the drug chart.

DRUG BLOOD LEVELS

Figure 1.3. Second page of drug chart: once only medicines and loading doses prescription section with therapeutic drug monitoring. The top page saying drugs not administered belongs to the last page of the drug chart that is A4 size.

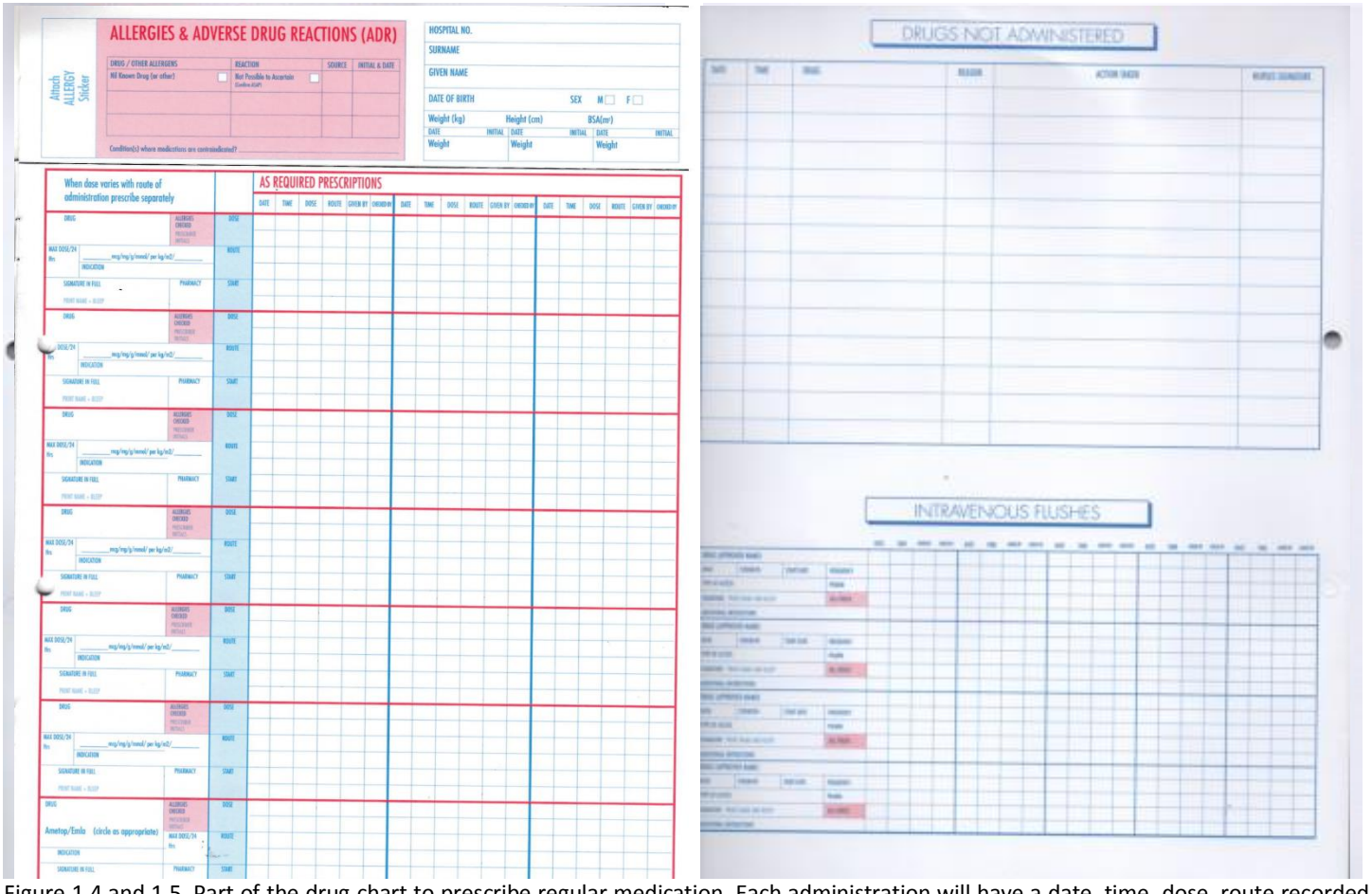


Figure 1.4 and 1.5. Part of the drug chart to prescribe regular medication. Each administration will have a date, time, dose, route recorded by the administering staff. Each change of dose or frequency is noted in the second left column. The pharmacist validates the prescription by writing in green in the pharmacy section (top right).

At the bottom of the page there are numbers coded to represent reason for not giving a drug and this code is linked with the last page of the drug chart.

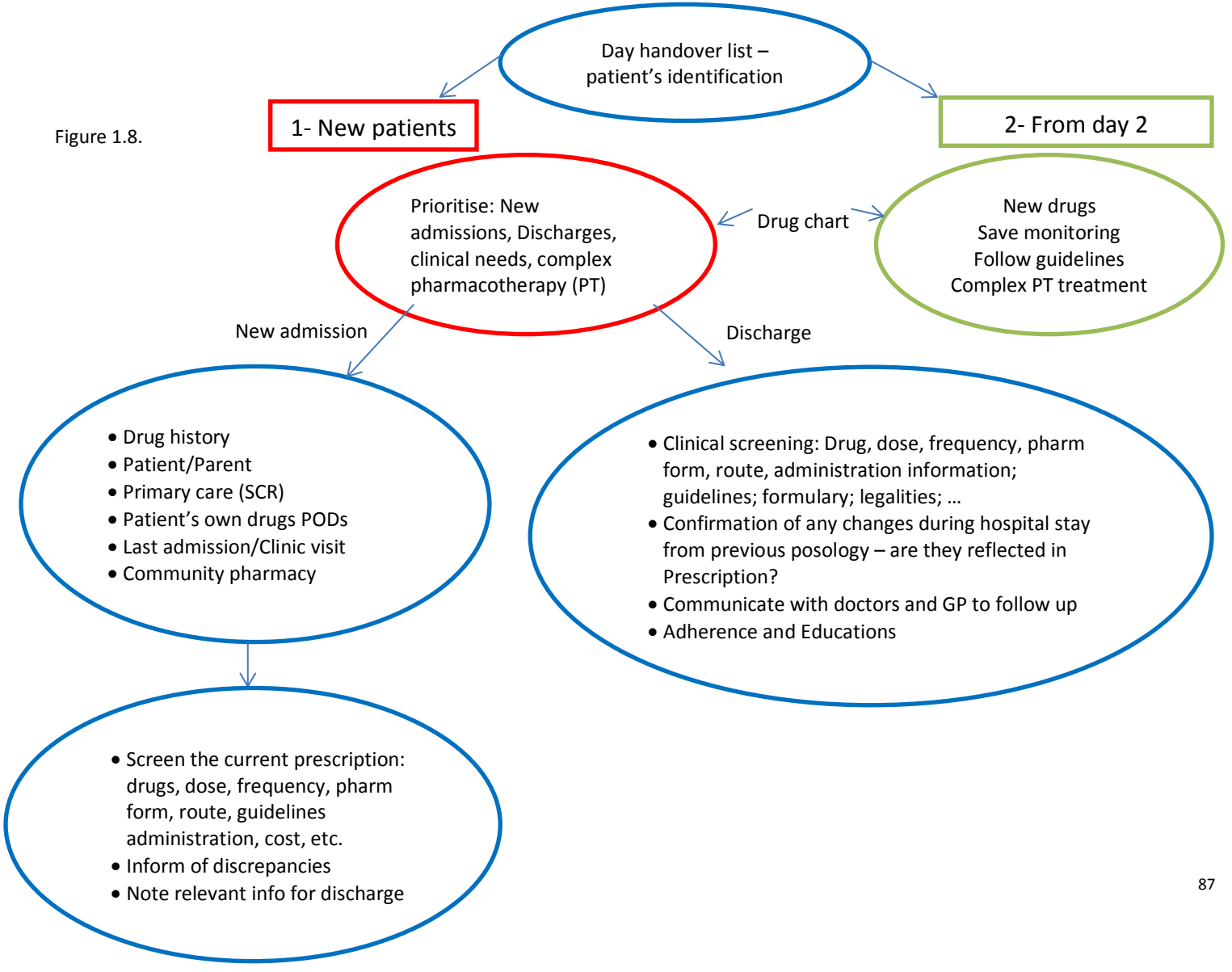
The drug chart is manually manipulated and is attached to the patient's notes together with other clinical information relevant to the patient. Each drug chart has been designed for 14 days duration. Patients staying longer will need a reboard with a new chart.

The fields to complete in a prescription are manually filled in and omissions are likely to happen. The drug charts are in continuous design with feedback from prescribers, governance team and pharmacist to make sure the risk of error is mitigated.

Next page's flow chart (Figure 1.8) summarises the main daily tasks of a hospital pharmacist in a ward visit/ward round in the UK.

The pharmacist has access to the handover list of the patients admitted to the ward. This helps identify which speciality the patient is under and clinical situations that require more or less pharmacological input. The handover list is also helpful to pharmacist as aids prioritising new patients. Patients admitted days before will also be seen by pharmacist to ensure that if new medicines have been added to the prescription that they are clinically screened.

Figure 1.8.


Day handover list – patient's identification
1- New patients
2- From day 2
Prioritise: New admissions, Discharges, clinical needs, complex pharmacotherapy (PT)
Drug chart
New drugs
Save monitoring
Follow guidelines
Complex PT treatment
New admission
Discharge
• Drug history
• Patient/Parent
• Primary care (SCR)
• Patient's own drugs PODs
• Last admission/Clinic visit
• Community pharmacy
• Clinical screening: Drug, dose, frequency, pharm form, route, administration information; guidelines; formulary; legalities; …
• Confirmation of any changes during hospital stay from previous posology – are they reflected in Prescription?
• Communicate with doctors and GP to follow up
• Adherence and Educations
• Screen the current prescription: drugs, dose, frequency, pharm form, route, guidelines administration, cost, etc.
• Inform of discrepancies
• Note relevant info for discharge

1.7. Quality of the pharmacotherapy and patient safety.

The Department of Health publication '*An organisation with a memory'* mobilised the patient safety movement in the British National Health System (NHS)[84]. The report reviewed the growing body of international evidence on patient safety. It drew attention to the scale and pattern of potentially avoidable patient safety incidents (any unintended or unexpected incident that could have or did lead to harm for one or more patients receiving NHS-funded healthcare) and the devastating consequences these can have on patients, their families and the healthcare staff involved. The report also acknowledged that, as in many other countries, there has been little systematic learning from these patient safety incidents and service failure in the NHS.

It is difficult to accurately estimate the extent of unintended harm to patients across the NHS from the current studies. There is likely to be significant under-reporting and inadequate documentation of patient safety incidents within medical records (the usual source of information on unintended harm for most studies).

On the best available data in England, extrapolating from a small study in two acute care trusts based in London, it is estimated that around 10% of patients (900,000 using admission rates for 2002/3) admitted to NHS hospitals have experienced a patient safety incident, and that up to half of these incidents could have been prevented[85]. This study also estimated

that 72,000 of these incidents may contribute to the death of patients, although it is unclear what proportion of this number would die as a direct result of the incident.

In the ENEAS study, the most recent Spanish national study about adverse events in hospitalised patients, the incidence of adverse events was 8.4%, being medicines responsible of 37% of the effects but also the half of them were preventable[86]. Studies in the United States have found that between 44,000 and 98,000 incidents are estimated to contribute to patient deaths[87,88]. This is viewed by many commentators as under-estimating the extent of the problem. Studies in Australia[89], New Zealand and Denmark[90] have suggested similar findings.

Adverse events are an emerging problem in medication's field. Consequences of harm caused by drugs affect directly patients and services with an increase in costs[91]. Hence professionals and commissioners are keen on offer a safe, efficient and effective patient's care and patient' safety has become a key factor in quality of health systems.

The Audit Commission report in the UK, *A Spoonful of Sugar*, emphasised in 2001 that NHS trust boards should recognise that medicines management was a significant part of clinical governance responsibilities. In this report it was acknowledge that medication errors occur too often and their effect on patients and NHS costs can be profound; additionally many patients do not take their medicines as recommended once they leave hospital[92]. Ten years after another finance and safety concern

looked at homecare medication in the UK, *The Hackett report* (2011), which made a list of recommendations to improve the financial and clinical governance arrangements for patients receiving medicines in the UK via the homecare route[93].

The *Carter report* (2015) acknowledged the need of the hospital pharmacist to spend greater time in clinical services as part of the optimisation resources of the NHS[94] and a hospital model was published in October 2016[95].

In general, all of the above reports intend to build a safer health care system at minimal possible cost utilising best resources available.

In fact, research around patient safety has highlighted that the majority of staff try to create a safe environment, preventing things from going wrong. Despite some high profile cases the overwhelming majority of incidents are not caused by malicious intent or even lack of competence on the part of the individual delivering the care[96], the best people can make the worst mistakes[97].

Having a safety culture encourages a working environment where many components are taken into account and recognised as contributing to an incident or to the events leading up to it. This moves the investigator away from focusing blame on individuals and looks at what was wrong with the system in which the individuals were working. This is called the systems approach[98].

Therefore the previous National Patient Safety Agency (NPSA) now known as the National Reporting and Learning Service (NRLS), presented an overview of the **7 key steps** required to achieve a safer organisation. The first 3 steps introduce the concepts, methods, research and practical tools in relation to developing a safety culture (step 1), establishing a strong focus on patient safety throughout the organisation (step 2) and integrating risk management systems (step 3). The following steps describe national and local reporting requirements (steps 4), patient and public involvement in safety (step 5), the root cause analysis approach to incident investigation (step 6) and transferring lessons to solutions (step 7). Every day more than a million people are treated safely and successfully in the NHS. However the advances in technology and knowledge in recent decades have created an immensely multifaceted healthcare system. Patient safety is such an important concept that it is vital that healthcare staff can progress towards delivering this safety agenda. The 7 steps provide a guide to help them achieve this[99].

Nonetheless it is widely acknowledged that the term 'error', when investigating an incident and attributed to humans, implies blame and responsibility. Adopting a positive culture of learning from mistakes might lead to reporting open and sharing what can be learnt. Figure 1.9 shows the circle of safety in 7 steps.

Figure 1.9. Circle of safety modified from NRLS seven steps.

1.7.1. Medication errors. Causes and consequences.

In healthcare practice, an error is a mistake act that causes or could cause harm to patients due to commission or omission in the clinical practice of the healthcare professionals. This mistake might contribute to an adverse incident[100,101].

According to the FDA a medication error is *"any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including* ***prescribing****; order communication; product labelling, packaging, and nomenclature;*

compounding; dispensing; distribution; administration; education; monitoring; and use."

Medication errors are one of the most common types of medical error[102]. It has been estimated that 1–2% of patients admitted to US hospitals are harmed as a result of medication errors, the majority of which are errors in prescribing[103,104]. In a study about medication errors carried out in a Valencian Hospital (Spain), the global percentage of potential medication errors was 7.2% and 4.4 % of them reached the patient[105]. The safe administration of medicines is an important part of ensuring patient care. Nurses are the professionals most likely to administer medication and the Nursing & Midwifery Council (NMC) recognises that it is not a mechanistic task to be performed in strict compliance with the instructions of the prescriber, but requires thought and the exercise of professional judgment[106].

The administration of medicines has been identified as a source of risk to patients. The National Reporting and Learning System highlights that the most frequently reported source of medication errors are wrong dose, omitted or delayed medication and administration of the wrong medicine[107]. This has prompted many organisations to adopt the **'5 rights'** approach to medication administration: Right patient, Right drug, Right dose, Right route, Right time (Jones 2009). Some types of errors, such as maladministration of insulin, are now classed by the Department of Health (DH) as 'never events' which are considered to be unacceptable and eminently preventable. Of the 14 current 'never events' (previously

25), 5 relate to medication issues[108]**.** Therefore we can say that the rights of medication administration are the foundation for medication safety, however we must take into account that priot administering a medicine, we need a prescription. Once the right prescription has been written, the nurse following the original five rights of medication administration will give (1) the *right patient* the (2) *right drug* (3) with the *right dose* via (4) the *right route* at the (5) *right time*.

Medicines reconciliation is defined as 'being the process of identifying the most accurate list of a patient's current medicines –including the name, dosage, frequency and route – and comparing them to the current list in use, recognizing any discrepancies, and documenting any changes, thus resulting in a complete list of medications, accurately communicated[109]. Reliable reconciliation of medicines at admission and discharge from hospital is key to reducing unintentional prescribing discrepancies at transitions of healthcare[110]. Therefore multiple transitions of the patient are critical factors for conciliation errors, being a subtype of medication errors produced by these transition.

Prescribing errors are considered a type of medical errors but prescribing faults, a subset of medication errors, should be distinguished from prescription errors. A prescribing fault is a failure in the prescribing (decision-making) process that leads to, or has the potential to lead to, harm to the patient. The converse of this, *balanced prescribing* is *the use of a medicine that is appropriate to the patient's condition and, within the*

limits created by the uncertainty that attends therapeutic decisions, in a dosage regimen that optimizes the balance of benefit to harm.[111]

A prescription error is a failure in the prescription writing process that results in a wrong instruction about one or more of the normal features of a prescription. The normal features include the identity of the recipient, the identity of the drug, the formulation, dose, route, timing, frequency, and duration of administration[111].

In fact prescribing errors are a well-recognised cause of adverse incidents and have a direct effect on patients[112]. This impacts on the doctor-family relationship and results in breakdown of trust and communication[113].

In one study in a UK hospital, pharmacists identified and rectified a prescribing error in 1.5% of all medication orders written, of which about one quarter were potentially serious and likely to result in patient harm[114].

In another more recent study also in the UK, the incidence of prescribing errors was 8.4% and most of them occurred at hospital discharge[115].

Other recent reports of prescribing errors vary widely, from 5% to 81% of prescriptions[116,117]. A significant proportion of errors are believed to be caused not by system design features or software glitches, but by human factors, such as fatigue, selecting the wrong option, or entering the wrong patient information into an often cumbersome system. And although most prescribing errors are detected and resolved by pharmacists in both

the inpatient and community settings[118,119,120], some still slip through the entire medication use chain, making it all the way to the patient.

In 2000, the UK Department of Health report recommended that serious errors in the use of prescribed drugs should be reduced by 40% by 2005[121]. A report from the UK Audit Commission[122] emphasised the problem of medication errors in UK hospitals and highlighted the importance of hospital pharmacists in preventing them.

Typification of medical errors.

The best way to understand how medication errors happen and how to prevent them is to consider their classification, which can be contextual, modal, or psychological[111]. Generally speaking contextual classification deals with the specific time, place, medicines, and people involved; modal classification examines the ways in which errors occur (e.g. by omission, repetition, or substitution) and psychological theory[123] explains events rather than merely describing them.

Modal classification seems to be the best way to analyse the cause of medication errors. They are classified in two types:

- Committed errors (or real): where there was an actual mistake in the prescription due to lapse, lack of knowledge, lack of procedures of checking, training need, etc.
- Omitted errors or missing errors caused by information omitted.

And both of them have the 5 rights as subtype:

1. drug
2. dose
3. frequency
4. pharmaceutical form
5. route of administration.

Any evitable occurrence relating to the inappropriate use of drugs whilst they are controlled under an environment with healthcare professionals is considered a medication error. Adverse effects are excluded from the concept of medication error however adverse events can be a consequence of a medication error. The possibility of committing medication errors are multiple and they have been analysed in different studies[124,125,126,127].

Effective error management requires an understanding of the varieties of human error and the conditions likely to promote them. If human error factors (such as administering the wrong dose of a prescribed drug) are identified, organisations can start to find solutions that predict or prevent it and make changes that maximise performance rather than set people up to fail. In addition the causes of any patient safety incident extend far beyond the actions of the individual healthcare staff directly involved, and are often out of their control. And while human error might immediately precede an incident, in a technically and socially complex system like healthcare, there are usually entrenched systemic factors at work.[128]

Errors occur in health care as well as in every other very complex system that involve human beings. The message in *To Err is Human* is that

preventing death and injury from medical errors requires dramatic, system wide changes[129]. Among three important strategies—preventing, recognizing, and mitigating harm from error—the first strategy (recognizing and implementing actions to *prevent* error) has the greatest potential effect, just as in preventive public health efforts. This report *To err is human*, was published by *The institute of* Medicine of USA in 1999 and was reviewed 7 and 10 years after, always with the same message in medication as an area that needs constant surveillance and improvement.

Medication errors are a multidisciplinary problem and a multidisciplinary approach is required in order to reduce their incidence[130]. And although medication errors can occasionally be serious, they are not commonly so and are often trivial. However, it is important to detect them, since system failures that result in minor errors can later lead to serious errors. Reporting of errors should be encouraged by creating a blame-free, non-punitive environment. Avoiding medication errors is important in balanced prescribing, which is the use of a medicine that is appropriate to the patient's condition and, within the limits created by the uncertainty that attends therapeutic decisions, in a dosage regimen that optimizes the balance of benefit to harm. In balanced prescribing the mechanism of action of the drug should be married to the pathophysiology of the disease[131].

Causes and consequences of errors.

The National Reporting and Learning Service (NRLS) analysed the 7 steps published in order to prevent mistakes to happen.

The seven steps to patient safety causal factors are classified into the following groups[132]:

- **Active failures:** these are actions or omissions that are sometimes called 'unsafe acts'. They are actions by frontline healthcare staff who are in direct contact with patients, and include slips, lapses, mistakes or violations of a procedure, guideline or policy. Usually short lived and often unpredictable, they are influenced by latent system conditions and contributory factors (see below) such as stress, inadequate training and assessment, poor supervision or high workload. An examples of active failures could be an infusion bag with added potassium is incorrectly stored on the first shelf (for saline only) rather than the normal place on the second shelf. In an emergency a staff member picks up the bag from the first shelf assuming it is saline and gives the patient the wrong bag;
- **Latent system conditions:** These are the underlying rather than immediate factors that can lead to patient safety incidents. They relate to aspects of the system in which people work. They are usually actions or decisions taken at the higher levels of an organisation, which seem well thought out and appropriate at the time but can create potential problems within the system. These factors can lie dormant and unrecognised for some time. Alternatively they may be recognised but changing them is not a priority. The latent conditions combined with local conditions (active failures and contributory factors) create the potential for

incidents to happen. Examples of latent system factors include decisions on:

–**Planning:** fixed staffing levels may be adequate until extreme situations occur, such as more than the usual numbers of staff are on sick leave, or there are more than the usual number of critically ill patients;

–**Designing:** designing a new clinic, practice, ward or diagnostic centre without considering vulnerable groups, such as children or mental health patients, and leaving dangerous equipment within their reach;

–**Policy-making:** having a strict take-home policy for drugs, which doesn't take into account difficult times to get to a pharmacy (holidays such as Christmas) or unlicensed medication that may not be local stock items;

–**Communicating:** having only a limited reporting structure for patient safety incidents, which means vital lessons are not learned across the organisation.

- **Violations:** these are when individuals or groups deliberately do not follow a known procedure or choose not to follow a procedure for a number of reasons, including:

  – they may not be aware of the procedure;

  – the situation dictates a deviation;

– it has become habit;

– the procedure has been found not to work;

– the procedure has been surpassed by a new one but it has yet to be rewritten.

- **Contributory factors:** these can contribute to an incident in relation to:

  –**Patients:** unique to the patient involved in the incident, such as the complexity of their condition or factors such as their age or language;

  –**Individuals:** unique to the individual involved in the incident. They include psychological factors, home factors, and work relationships;

  – **Tasks:** these include aids that support the delivery of patient care, such as policies, guidelines and procedural documents. They need to be up to date, available, understandable, useable, relevant and correct;

  –**Communication:** these include communication in all forms: written, verbal and non-verbal. Communication can contribute to an incident if it is inadequate, ineffective, confusing, or if it is too late. These factors are relevant between individuals, within and between teams, and within and between organisations;

–**Team and social factors:** these can adversely affect the cohesiveness of a team. They involve communication within a team, management style, traditional hierarchical structures, lack of respect for less senior members of the team and perception of roles;

– **Education and training:** the availability and quality of training programmes for staff can directly affect their ability to perform their job or to respond to difficult or emergency circumstances. The effectiveness of training as a method of safety improvement is influenced by content, delivery style, understanding and assessment of skill acquisition, monitoring and updates;

–**Equipment and resources:** equipment factors include whether the equipment is fit for purpose, whether staff know how to use the equipment, where it is stored and how often it is maintained. Resource factors include the capacity to deliver the care required, budget allocation, staffing allocation and skill mix;

–**Working conditions and environmental factors:** these affect ability to function at optimum levels in the workplace, and include distractions, interruptions, uncomfortable heat, poor lighting, noise and lack of or inappropriate use of space.

The seven steps causes of errors can be applied to any discipline and in *grosso modo* medical causes are:

1. Educational- due to lack of knowledge
2. Communication- due to failure in communicating properly
3. Technological- due to aspects of the electronic components allied to the health care system
4. Organizative- due to a decline of the workload organisation
5. Human- due to lapse, tiredness.

However and from a pharmacy perspective the most common cause of errors are the ones described in Table 1.7.

Table 1.7 Most common specific errors from a pharmacy perspective.

- Unawareness of medication history of the patient and clinical history
- Use of an inappropriate drug
- Wrong drug due to similar name or package
- Wrong dose
- Wrong frequency
- Unawareness of drug interactions
- Wrong calculation in obese, paediatrics, elderly or renal patients
- Dotted numbers misplaced
- Wrong pharmaceutical form
- Wrong route of administration
- Use of non standard abbreviations
- Insufficient communication between healthcare professionals.

Regardless of the cause or the type of the incident there might be some mitigating factors, whether actions or inaction such as chance or luck, may have mitigated or minimised a more serious outcome. When investigating these factors it is important that these are drawn out so that the lessons can be used to support and promote good safety practice. Figure 1.5 represents how human errors can reach the patient if the steps to follow the process of medication prescribing are missed.

The consequences of a medical error define the impact an incident can have, ranging from no harm to the patient to various levels of severity of harm: low, moderate, severe and death[96]. Studies classify consequences of errors in severity values/scales. Regardless of the scale a consequence of medical error is that health care providers at all training levels experience feelings of guilt, disappointment, fear and sense of inadequacy of varying degree.[133,134] After all, the effects of harming a patient can be widespread and there can be devastating emotional and physical consequences for patients and their families.

As per the 7 steps and current practice within the NHS Hospitals consequences should be shared to learn in the best possible ways and causes need investigation to prevent similar incidents to occur again.

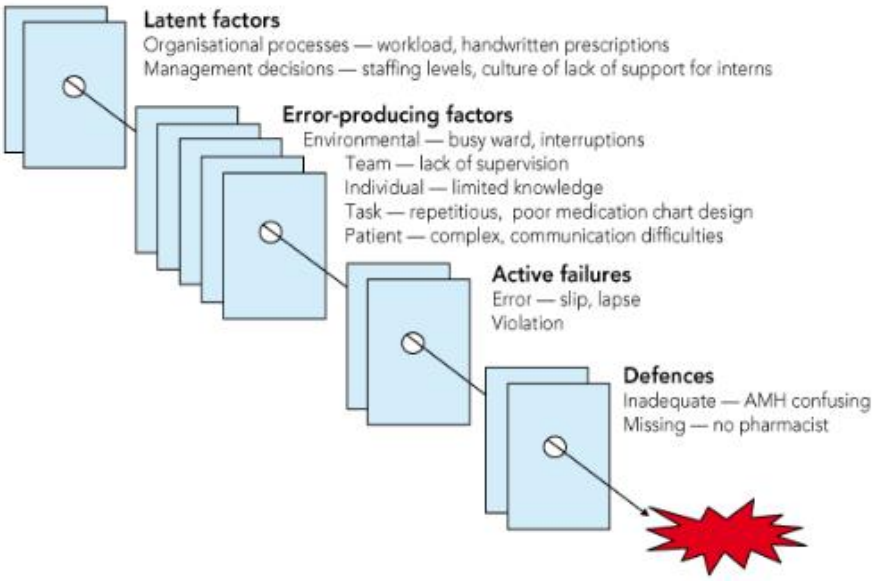


Figure 1.5. Incident analysis framework, adapted from Reason J' model of accident causation[135].

1.7.2. Safety actions and improvement strategies.

The seven steps to patient safety's document overview the National Reporting and Learning Service (NRLS)'s detailed guide to **good practice**, which covers building a safer culture and managing, reporting and learning from **patient safety incidents**. It sets out the **seven steps** that NHS organisations should take to improve patient safety. These are summarised in Table 1.8.

Identifying safety actions and implementing strategies is an essential part in the safety of the patient. But most importantly is that staff actively engage in with a **safety plan** and have a clear understanding of patient

safety improvement and the role they play in achieving this. Engagement is essential in order to create synergy and integrated working.

Table 1.8. The Seven steps to patient safety and each one's aim.

Step 1 Build a safety culture	Create a culture that is open and fair
Step 2 Lead and support your staff	Establish a clear and strong focus on patient safety throughout your organisation
Step 3 Integrate your risk management activity	Develop systems and processes to manage your risks and identify and assess things that could go wrong
Step 4 Promote reporting	Ensure staff can easily report incidents locally and nationally
Step 5 Involve and communicate with patients and the public	Develop ways to communicate openly with and listen to patients
Step 6 Learn and share safety lessons	Encourage staff to use root cause analysis to learn how and why incidents happen
Step 7 Implement solutions to prevent harm	Embed lessons through changes to practice, processes or systems

A safety plan sets out the key patient safety aims, goals or prioritised areas of improvement work that need to be reliably implemented and spread in order to achieve the high level strategic aims and patient safety outcomes. Normally these plans start with a focus on identified pilot areas, taking a multidisciplinary team based approach and where possible informed by current local data that identifies the size and scale of the problem and therefore informs us of where best to focus improvement effort to maximise impact.

The Table 1.9 summarises some of the requirements to successfully implement safety plans.

In the UK, NHS organisations have a Governance team monitoring closely incident reports. The use of medicines is a complex system and patients are at the end of the chain, therefore pharmacists adopt a crucial role in improving drug usage and preventing prescribing errors ensuring safety of the patient. The use of medicines' system includes different episodes of risks of errors as well as quality defects that can be a cause of harm in the health of the patient. This situation requires the establishment of a quality system to assess risks and prevent errors that may occur in patient's pharmacotherapy but also preventing errors in each phase of the pharmacotherapy process (prescription, screening, labelling, preparation, dispensing, administering the medicine).

Table 1.9. Main requirements for a successful implementation plan.

- Strong, clear and visible clinical leadership attention to patient safety.
- Multidisciplinary team approach to priority areas.
- Infrastructure and dedicated resources to establish a patient safety improvement team.
- Capability of key staff groups in patient safety and quality improvement to support implementation.
- Engagement, ownership and involvement of all staff.
- Organisational commitment and learning about medical errors encouraging.
- Dedicated budget for Patient Safety.

- Supportive, learning environment and culture to assist with the sharing of knowledge, skills and experience to effect behavioural changes
- Recognition and reporting of errors and near misses as well as identification of risks to patient safety without judgment or placement of blame.
- Proactive involvement of patients, relatives and carers in decisions about their health care promoting open communication about own experience. Feedback request.
- A dedicated patient safety communication plan, web resource and media support.
- An infrastructure, technological resource and dedicated data team to make collection, analysis of data and meaningful measurement for safety improvement from ward to board.

Furthermore and in a global way The Care Quality Commission (CQC) is the independent regulator of health and adult social care services in England. Their aim is to make sure health and social care services provide people with safe, effective, compassionate, high-quality care, and with regular inspections they encourage care services to improve. CQC monitors, inspects and regulate services to make sure they meet fundamental standards of quality and safety and their findings are published with information on the rating of the performance. It is obvious that CQC visits are taken seriously by healthcare professionals working in the NHS as their rating will be publised. After a CQC visit, they propose actions and targets consistent with the 7 steps of patient safety and NHS organisations to health care professionals are encouraged to pursue these objectives.

Safety actions are the aftereffect of a plan after the incidents have been analysed. Often root cause analysis (RCA) are needed in safety investigations. A RCA is a structured method used to analyse serious incidents; as an individual RCA is essentially a case study of a specific error (unexpected event), analysis of multiple RCAs performed at different institutions may help identify patterns of error and point the way toward solutions. There are different ways to implement strategies to improve such as daily prompt emails, posters with relevant information, checklist of most common risk areas to assess, regular meetings, etc. In order to help the investigating process in a RCA, it is important to understand the tools needed for the investigators:

- gather and map information;
- identify care and service delivery problems;
- analysing to identify contributory factors and root causes;
- generate solutions;
- log, audit and learn from investigation reports

There may be more than one causal factor in any incident. Therefore a root cause analysis is a fundamental component of which is to understand and identify the causal factors that influence risk and safety. The Table 1.10 is an example of action plan template suggested by NPSA, and recommends pointing the names of the persons to action certain tasks with deadlines to implement.

RCA is one of the tools that helps establishing a safety culture. It is necessary workers report incidents as well as learning/sharing from

errors. However from a constructive perspective sharing from positive actions that staff carry out is another category that can help learning patient safety but this vision has not been implemented widely.

Table 1.10. Example of Action plan template suggested by NPSA[136]

	Action 1	Action 2	More
Root cause			
Effect on patient			
Recommendation			
Action to address root cause			
Level for action (Org, Directorate, Team)			
Implementation by:			
Target date for implementation			
Additional resources required (time, money, other)			
Evidence of progress and completion			
Monitoring & evaluation arrangements			
Sign off - action completed date:			
Sign off by:			

Barts Health NHS use Datix© system to report incidents. The governance body for each speciality meets monthly to analyse each incident and they make sure reports are reviewed and actions are taken to prevent/reduce incidents. The UK has a culture of share the learning with relevant staff and design ways to implement safety environtment. The is a risk registrar too that is under the Governance body, in there the risk assessments that score a certain number are analysed to help preventing serious incidents or never events.

1.7.3. Quality and safety in the prescribing process in children with Cystic Fibrosis.

Safe administration of medication is a national priority. It is an essential standard of the Care Quality Commission[137] and NHS Litigation authority[138] in England, and a key outcome of the Scottish Patient Safety Programme[139] and 1000 lives plus safety programme in Wales[140]**.** Therefore it is important that all NHS Professionals' flexible workers are aware of their responsibilities with regards to medication administration. Not only nursing staff.

The complexity of CF disease and its pharmacology is also transfered to the different type of prescriptions that the medicines have to be prescribed in the UK. Despite doctors deciding best pharmacological treatment for the child, the prescription must be clear since it is the next step to confirm that best treatment will be administered. The prescription is the labelling precedent, hence the quality of this prescription should be considered to reach best and consistent information to patient, with a review of concomitant drugs too and the possibility of discontinuation of certain treatments. Considering some patients might take medication at school time, the community nurse administering the medication to CF children should also be advised of possible other drug therapies being discontinued, hence communication with primary care is also a very important factor.

The quality of the CF prescriptions for children that are frequently admitted to hospital should focus in the following aspects:

- The presence of the weight of the child in the prescription
- The presence of any of medicines that concord with associated pathologies in the discharge prescriptions as well as correct optimised dose/frequency.
- Pharmacokinetic aspects like drug interactions that might affect the pH of the stomach, concomitant medication that is liver metabolised (looking in to dose adjustment), dosing, and information on length of treatment.
- The clarity of the prescription that relates to antibiotics, either nebulised, oral or IV- when to stop and to restart.
- Duration of treatment, when the drug is newly started to ensure review of symptoms and effectiveness.
- Pharmaceutical forms, especially if there are particular drugs that the patient prefers, to help adherence.
- Any allergy information documented.

Table 1.11 summarises the main aspects that should be reviewed to achieve quality of the prescription for each drug/group of drugs.

Table 1.11. Main aspects to take into consideration to provide quality of CF prescriptions regarding main associated pathologies and group of drugs.

	Indication/ Omission	Pharmaceutical form	PK interactions	Duration
Pancreatinin enzymes	✓			
Fat soluble vitamins	✓	✓		
Gastro-intestinal drugs	✓	✓		

ABPA treatment with antifungals	✓	✓	✓	✓
Nebulised antibiotic	✓	✓		✓

Patient- related risk factors.

Paediatric patients have significant need for research and development into paediatric medicines. Only a small fraction of the drugs marketed and utilized as therapeutic agents in children have been clinically evaluated. The majority of marketed drugs are either not labelled, or inadequately labelled, for use in paediatric patients. The absence of suitable medicines or critical safety and efficacy information poses significant risks to a particularly vulnerable patient population. However, there are many challenges when developing medicines for the paediatric population and thia is reflected with the limited paediatric formulations in the market. The paediatric population is made up of a wide range of individuals of substantially varied physical size, weight and stage of physiological development[141].

A recent study in a London hospital aimed to quantitatively assess the level of medication error for paediatric inpatients on admission and discharge and to ascertain whether discharge summary information is sent to the GP in a timely manner but none of the standards set up were met, emphasising the need to develop better medicines reconciliation practice[142].

Previous research has acknowledged that paediatric patients are at risk of encountering medication errors including prescribing errors[143]. However there are not many studies in the UK that calculate the incidence of prescribing errors in the paediatric population.

A general definition of a prescribing error was developed for paediatrics[144] and the following factors were considered prescribing errors:

- Failure to communicate essential information
- transcription errors and the use of drugs
- formulations
- inappropriate doses

However, no studies have been found for quality prescribing in CF children, when polytherapy is a daily fact. Studies of pharmacists' interventions have been carried out in UK hospitals but little or none studies of pharmacists evaluating CF discharge prescriptions have been published.

Drug therapy related risk factors.

Patients admitted to IV therapy stop their nebulized antibiotics and in most of the cases patients are expected to restart them after the IV course. However, when the patient is due to be discharged, the information regarding restarting treatment with the nebulised antibiotics and prophylactic antibiotics (if they were on them prior to admission) can be missed, with the possibly of creating confusion to parents, especially

when the weight of the pharmacological treatment resides primarily in one member of the family: for instance if the main career is not present during discharge talks, if there is any pharmacological information given verbally that is not reflected in the prescription, this information might not be communicated.

Moreover, unfortunately there are not many different child friendly drugs in the market and very often pharmacists must find information for unlicensed use. Crushing and dispersing tablets is common practice when administering in children and palatability is not particularly pleasant in most of the cases. This often put parents under stress as they have certain knowledge of the disease and understandably expect quick solutions, as the multidisciplinary CF team is heavily involved. It is also a challenge for CF pharmacists when seeking unlicensed alternatives as not only do governance bodies expect any risk aspects of treatment being covered but in parallel commissioner bodies can be unhelpful with requests made to import overseas presentations that are licensed in other parts of Europe.

Below paragraphs reflect a description about specific drug therapy with antibiotics and its duration of with a potential cause of confusion, delay or error affecting patient's trust with the medical team and adherence (explain the need of greater information of CF disease when prescribing or screening a prescription):

Generally speaking prescriptions with antibiotics in the UK must includethe duration of treatment. If this was missing, the prescription

would automatically be queried by the pharmacist, leading to extra waiting time for the patient if waiting in community pharmacy. Also patient information leaflets dispensed with antibiotics described short-term treatment, which is not always the case in CF.

However a CF pharmacist or doctor would not necessary request to add any duration antibiotics if for instance the regime prescribed corresponded to a prophylactic regimen (easily identifiable via dosage or frequency) in a CF patient or if the treatment is to cover a pathogen that has been isolated, as patients can be on a course of antibiotics with treatment doses for 18 months, for instance in Non Mycobacterium Tuberculosis (NMT).

Hence one of the recommendations adding value to antibiotics prescribed for CF patients could be adding information like "long term antibiotic therapy" or "until further notice" or even stating the time "for 18 months, started on… or to finish/review by…".

Information added to the label of antibiotics for CF prophylaxis would allow a faster clinical screening for GPs prescribing in primary care, community pharmacies as well as parents being able to identify which is the antibiotic drug amongst the others in a cupboard.

From a CF perspective, it is accepted that doses and length of antibiotics may differ from standard dosing guidelines. Furthermore prescriptions for CF should have clear instructions as this would help adherence (by adding consistency with the instructions given to the careers/patient).

Prescriptions in primary care for antibiotics in CF children might be considered to contain prescribing errors when using standard electronic prescribing for age/weight and potentially community pharmacist can hold prescriptions due to what it might be thought "a prescribing error". However, in reality this prescribing might have been written intentionally as this dosage might be necessary and safe for a child with CF.

However and less importantly the drug therapy prescribed is a crucial factor in paediatric CF patients. Considering that not many paediatric friendly formulations are available, there is a risk of error if the prescription does not specify the formulation or the strength desired as often patient's administration are based with the volume. Another risk is the non-adherence if the child dislikes its flavour and all these factors need to be taken into consideration too in order to help with adherence.

Health care system risk factors.

Pharmacists, as well as doctors, are also involved in an in-depth learning curve when starting their career in hospital. Junior or foundation pharmacists are the ones on call and dealing with general queries. Sometimes they are required to cover specialty wards with little training provided.

Diseases like CF in the paediatric population and the polytherapy children have, can be a challenge for a junior trainee, either doctor or pharmacist. Prescribing on a busy ward, with lack of supervision plus other factors affecting prescribing are cause of prescribing mistakes[135].

Furthermore, the current system in the UK comprise a large variety of prescriptions. Inexperienced staff may cause incomplete medicines reconciliation despite best efforts to prescribe correctly, with the worry of omissions or wrong presentation/pharmaceutical affecting dosage and adherence.

While most authorities agree that the use of drugs outside the terms of their licence is a necessary part of paediatric practice, instances of more unconventional prescribing, and worries about potentially unnecessarily restrictive policies, are part of safety medicines incidents reports. Also, professionals often feel frustrated of the lack of paediatric friendly formulations in the UK market as well as cost pressures and documentation required (when they are available) to import them from European countries

The quality of a prescription for CF patients, is held to a different standards to that of a normal prescription. There are other factors that contribute to compliance problems in CF included patients receiving conflicting information[145]. It is clear that the paediatric population with CF is more vulnerable to medication errors.

The professionals involved in prescribing are junior doctors (ward prescribing, discharge summaries); senior doctors (named registrar in the UK); Consultants (clinic letters); CF independent prescribing pharmacist (clinic letters and homecare prescribing); GPs (acute and repeat prescriptions); Community pharmacist (prescriptions and over the counter products); ward pharmacist and junior pharmacist (for on call

queries). Specialist nurses often deal with the prescribing and should also be asked as well about what they consider quality in prescribing.

Educating the patient to better understand how the drug will help is also essential in adherence. But also community pharmacists and primary care doctors could benefit with some CF training or a hospital visit with specialist team if they have to deal with CF children in their clinics.

Specialist nurses, Consultants, junior doctors, dieticians and hospital pharmacist agree that better communication between the hospital, GP and local pharmacist would help patients to obtain medication in the community more efficiently.

Table 1.12 summarises the main patient, drug therapy and health system related risk factors associated within medication errors in children with CF.

Table 1.12. Main risk factors to drug errors in children with CF.

Patient- related risk factors.

- ✓ Lack of understanding of parents/teenage/child leading to failure to adhere to treatment.
- ✓ Complex administration dispositives (nebulisers).
- ✓ Need to individualised therapy (per body weight, body surface, indication or PK monitoring).
- ✓ Lack of diverse palatability of the drugs.
- ✓ Lack of child friendly preparations.
- ✓ Pharmaceutical forms not always adequate for gastrostomy use.
- ✓ Multiple hospital admissions with swapping nebulised antibiotic for intravenous.
- ✓ School time clashing with administration time.
- ✓ Conflicting information from media, other professionals, leaflets, etc.

Drug-therapy related risk factors

- ✓ Polypharmacy.
- ✓ Pathologies associated to CF with multiple specialties input in drug therapy.
- ✓ Routes of administration, as often CF children end up with gastrostomies in situ.
- ✓ Complex pharmacotherapy regime (alternating days, months, etc).

Health care system risk factors

- ✓ Multiple doctors involved in the prescribing process of medication.
- ✓ Multiple types of prescriptions leading to complicated gain of real drug history.
- ✓ Rotational junior staff in University Hospitals.
- ✓ Lack of knowledge of junior prescribers.
- ✓ Lack of knowledge of junior pharmacist.
- ✓ Continuous rotation of junior staff.

Hence it is important that experienced CF pharmacists deal with prescriptions for CF. It would be advisable that community pharmacist with CF patients as regular customers get specific education of the disease and its pharmacology in order to engage with patients/parents to help adherence as well as implement medicines optimisation.

Therefore, in CF prescriptions for children the following factors could also be considered as a quality aspect: essential medication not being omitted, allergies being confirmed, weight of the patient present in the prescription and fast communication with primary care (doctors and community pharmacists).

All professionals would agree that the aim of quality in CF prescriptions are: safety, effectivity, efficacy, cost management, patient's education to

reinforce and provide consistency to improve adherence. The quality standards to be set up in the CF prescribing environment would provide greater in-depth information if they were analysed per groups of professionals dealing with CF patients, which is a field to explore.

The Royal London Hospital for Children is a referral centre for paediatric CF spending a great time educating staff, parents and children. The centre work with a multidisciplinary team with a focus on patient's best interest. Currently there is dedicated consultant pharmacist who is developing guidelines and clinical information as well as being heavily involved with the education of parents/patients/staff in which the quality of the CF prescribing service improves and can project towards excellence.

Table 1.13 describes strategical and preventive actions that can mitigate risks factors described in Table 1. 12.

Table 1.13. Strategical and preventive actions.

- Specific designated staff liaising with prescriptions for homecare, drug chart, clinic letter medication list and discharge prescriptions.
- Clear pathway of education for rotational junior staff in University Hospitals for CF.
- Other specialty consultants treating pathologies associated with CF to liaise with specific staff.
- Limit prescribing and screening in junior doctors or pharmacist with no previous exposure to a limited number of CF patients.
- Continuous educational workshops for parents, relatives and teachers.
- Online skype workshops for CF adolescents to understand effects in failure to adhere to treatment.
- Research into different pharmaceutical forms for paediatric population.

However, the RLH referral centre is getting larger with more patients and being a teaching hospital there are continuously new rotational junior staff. From a prescribing perspective, there are also external factors to consider when prescribing such as different prescriptions and collection points of medication with potentially different staff providing information on the current pharmacotherapy. Moreover, CF patients undergo multiple hospital admissions and as the children grow medication dosage requires adjusting; polytherapy and associated pathologies also play a part in prescribing as well as junior and rotational staff involved in patient's care. The inspiration of this study relies on getting evidence to find out if there is room for improving the current discharge prescribing system and a depth knowledge on how pharmacy service can deliver best service for CF Team.

2. Objectives

2.1. Main objective

The main objective of this study conducted in hospitalised children with CF receiving IV antibiotics is:

- To improve the quality of the discharge prescription with the use of safety indicators in CF paediatric patients that are admitted to receive IV antibiotics treatment.

In order to achieve the main objective, the study was carried over within two periods: a retrospective phase and a prospective phase. Each period had into consideration the following specific objectives:

Retrospective phase.

- Evaluate quantitative and qualitatively the medication errors found in discharge prescriptions previously validated by a pharmacist.
- Evaluate quantitative and qualitatively the medication errors found in the discharge letters written after discharging the patient.
- Identify, classify and analyse the causes of medication errors found more frequently.
- Propose improvement recommendations to the prescribing professionals and design strategies to implement these recommendations in clinical practice.

Prospective phase

- Evaluate quantitative and qualitatively the medication errors found during patients' admission.

- Evaluate quantitative and qualitatively the medication errors found in discharge prescriptions previously validated by a pharmacist.
- Evaluate the impact of the improvement recommendations carried over.

3. Methods and Materials

3.1. Design.

Ambispective study conducted in two phases:

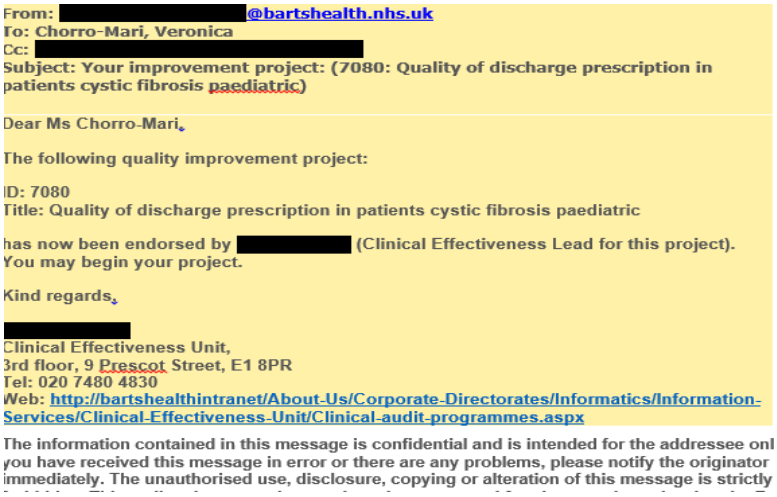
- A retrospective longitudinal observational descriptive study from January 2013 to December 2014 (24 months).
- A prospective longitudinal quasi-experimental study from May 2016- December 2016 (8 months).

3.2. Study setting.

Barts Health (BH) NHS Trust is the association of five different NHS University hospitals in London. BH is a tertiary Regional CF centre for adults and children. The paediatric centre is based at The Royal London Hospital (RLH) and CF patients are looked after by the paediatric respiratory department until the children reach 16 years old, which is when the transition process to adult CF clinics occurs.

Clinical Effectiveness Unit at Barts Health NHS Trust granted permission to commence a retrospective and prospective study.

The study was registered within the Clinical Effectiveness Unit at Barts Health NHS Trust. The number given for this study was ID: 7080. Figure 3.1 corresponds to the consent given for the study to take place.



From: [redacted]@bartshealth.nhs.uk
To: Chorro-Mari, Veronica
Cc: [redacted]
Subject: Your improvement project: (7080: Quality of discharge prescription in patients cystic fibrosis paediatric)

Dear Ms Chorro-Mari,

The following quality improvement project:

ID: 7080
Title: Quality of discharge prescription in patients cystic fibrosis paediatric

has now been endorsed by [redacted] (Clinical Effectiveness Lead for this project).
You may begin your project.

Kind regards,

[redacted]
Clinical Effectiveness Unit,
3rd floor, 9 Prescot Street, E1 8PR
Tel: 020 7480 4830
Web: http://bartshealthintranet/About-Us/Corporate-Directorates/Informatics/Information-Services/Clinical-Effectiveness-Unit/Clinical-audit-programmes.aspx

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immediately. The unauthorised use, disclosure, copying or alteration of this message is strictly

Figure 3.1. Consent received by Clinical Effectiveness Unit to start study

3.3. Sources of information.

Seven sources of information were used in order to analyse the prescription at discharge and also to conciliate medication on admission:

1. Electronic Prescribing Records (EPR, from BT®): this document was used in the retrospective study. This is the document written by the doctor at the time of discharging the patient from the hospital, and the prescribing medication is validated by a pharmacist. This document is sent to primary care doctors and given to parents of patients the day of discharge. This was the official document in 2013 and 2014 used when discharging a patient admitted at the RLH. Figure 3.2 represents a print screen

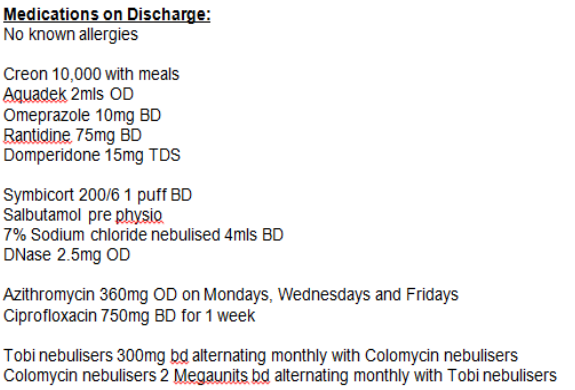
example from the Electronic prescribing system used during the time of the retrospective study.

Drug Name	Route	Dose	Directions/Frequency	No Days Supply	Continue?	Drug Location
CREON Capsule 10,000	PO	1 capsul	with meals and snacks	14	Yes-GP	Ward
AQUADEKS Liquid Paediatric	PO	2ml	Once a day	14	Yes-GP	Ward
RANITIDINE Syrup 75mg in 5ml	PO	150mg	Twice a day	14	Yes-GP	Ward
OMEPRAZOLE Capsule 10mg	PO	10mg	Twice a day	14	Yes-GP	Ward
SALBUTAMOL Inhaler 100micrograms/puff	INH	2-4puffs	pre-physio and when	14	Yes-GP	Ward
DOMPERIDONE Suspension 5mg in 5ml	PO	15mg	Three times a day	14	Yes-GP	Ward
SYMBICORT Turbohaler 200/6	INH	1 puff	Twice a day	14	Yes-GP	Ward
DORNASE ALFA Nebuliser solution 2.5mg in 2.5ml	INH	2.5mg	Once a day	14	Yes-GP	Patient
SODIUM CHLORIDE Nebuliser solution 7% 4ml	INH	4ml	Twice a day	14	Yes-GP	Ward
AZITHROMYCIN Suspension 200mg in 5ml	PO	400mg	Once a day on Mondays,	14	Yes-GP	Ward
ACETYLCYSTEINE Granules 200mg	PO	1 sachet	Up to three times a day	14	Yes-GP	Ward
COLISTIMETHATE SODIUM (COLISTIN) Injection 1megaunit	INH	1 megau	Twice a day via nebuliser-	14	Yes-GP	Patient
CIPROFLOXACIN Suspension 250mg in 5ml	PO	750mg	Twice a day	7	No	Dispensary

Figure 3.2. Example of EPR©, from British Telecom (BT).

2. Discharge letter (free type word version): is a comprehensive word document recording the admission time of the child's clinical situation, microbiological antibiograms, blood tests, spirometer results, etc. In this document there is a medication section with the list of the medicines prescribed on discharge. This is not a prescription document and therefore pharmacists do not validate the section where the medicines are listed. This document is not the official document used for discharging the patient but it is extremely useful as it includes sections for

following up disease progress. This document is also sent to primary care doctors and to parents of patients as soon as possible after the day of discharge. This document was only studied in the retrospective study. Figure 3.3 is a print screen of a patient's discharge letter section for medication at discharge.



Medications on Discharge:
No known allergies

Creon 10,000 with meals
Aquadek 2mls OD
Omeprazole 10mg BD
Rantidine 75mg BD
Domperidone 15mg TDS

Symbicort 200/6 1 puff BD
Salbutamol pre physio
7% Sodium chloride nebulised 4mls BD
DNase 2.5mg OD

Azithromycin 360mg OD on Mondays, Wednesdays and Fridays
Ciprofloxacin 750mg BD for 1 week

Tobi nebulisers 300mg bd alternating monthly with Colomycin nebulisers
Colomycin nebulisers 2 Megaunits bd alternating monthly with Tobi nebulisers

Figure 3.3. Medication list example in a Discharge letter

3. Electronic prescribing (CRS (Clinical Records System), from Cerner Millenium®): CRS contains clinical information with a prescribing section integrated in the same system. This document was installed in the place of the study during 2015 and was used to study the electronic prescribing in the prospective study. Figure 3.4 represents an example of CRS from a print screen and Figure 3.5 shows the final transcribed CRS prescription in the printable document version.

Current Medication and Route	Dose	Frequency	No. Days	Prescription Drugs to Continue	Verified by Pharmacist	Supply by Pharmacist	Pharmacy Comment
Promixin (NEB)	0.5	Twice Daily	14	Yes	Yes	No - Patient's Own	Patient: Homecare Dhx-
Bramitob (NEB) tobramycin	300mg	Twice Daily	14	Yes	Yes	No - Patient's Own	DHx:Pt[redacted]omecare-
Azithromycin (PO)	250mg	Three Times a	14	Yes	Yes	No - Patient's Own	DHx-PODs
Salbutamol 100mcg (INH)	2 puffs	Twice Daily	14	Yes	Yes	No - Patient's Own	Dhx-PODs
Dornase Alfa (NEB)	2.5mg	Evening	14	Yes	Yes	No - Patient's Own	DHx-PODs[redacted]
N-acetylcysteine 20% (NEB)	200mg	Twice Daily	14	Yes	Yes	No - Patient's Own	DHx-PODs (1mL to be
Seretide 125 (INH)	2 puffs	Twice Daily	14	Yes	Yes	No - Patient's Own	Dhx-PODs
Omeprazole (PO) capsules	20mg	Twice Daily	14	Yes	Yes	No - Patient's Own	Dhx-PODs
Domperidone (PO) tablets	10mg	3 X Per Day	14	Yes	Yes	No - Patient's Own	Dhx-PODs
Ranitidine (PO) tablets	75mg	Twice Daily	14	Yes	Yes	No - Patient's Own	Dhx Relabel on ward- GP
AquADEKS Chewable Tablets	one tablet	Twice Daily	14	Yes	Yes	No - One Stop	DHx-OSD-ward
Montelukast (PO) chew tablets	5mg	Evening	14	Yes	Yes	No - Patient's Own	Dhx-PODs

Note that the CRS system needs manual typing of the name of the drug and route, as well as dosage. There is no designated space for pharmaceutical form and this has to be entered in the space for the drug too. Furthermore, the space for communication has a limited number of characters and often the information has to be entered in different separated lines under pharmacy comments. This system was implemented during 2015 at the RLH and was used to study the prospective discharge electronic prescriptions.

Figure 3.4. CRS® Discharge TTA* example from a print screen.
*TTA: To take away (medication patient needs to take home on discharge).

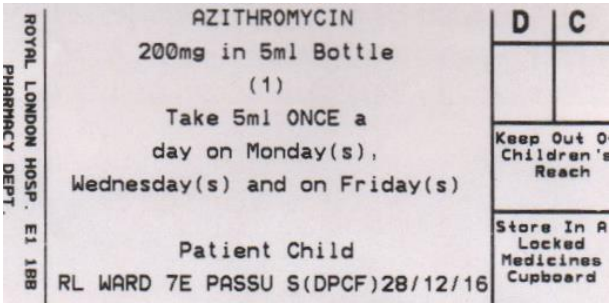
Drugs on Discharge:

Current Medication and Route	Dose	Frequency	No. Days	Cont.	Pharm Verify	Pharmacy Comments
Promixin (NEB)	0.5 megaun its	Twice Daily	14	Yes	Yes	Patient: Homecare Dhx- alternating monthly with Bramitob
						GP: No longer prescribed Clenil, ursodeoxycholic acid or cholecalciferol (changed in clinic some time ago. Also Promixin comes from Homecare not from GP (should be amended form repeat too)-Ranitidine dose should be 75mg BD (Please amend repeat Px too) [redacted]
Bramitob (NEB) tobramycin	300mg	Twice Daily	14	Yes	Yes	DHx- [redacted] A Homecare- Alternating monthly with Promixin
Azithromycin (PO)	250mg	Three Times a Week	14	Yes	Yes	DHx-PODs
Salbutamol 100mcg (INH)	2 puffs	Twice Daily	14	Yes	Yes	Dhx-PODs
Dornase Alfa (NEB)	2.5mg	Evening	14	Yes	Yes	DHx-PODs [redacted] Homecare
N-acetylcysteine 20% (NEB)	200mg	Twice Daily	14	Yes	Yes	DHx-PODs (1mL to be mixed with 2-3mL of WFI and nebulise BD)
Seretide 125 (INH)	2 puffs	Twice Daily	14	Yes	Yes	Dhx-PODs
Omeprazole (PO) capsules	20mg	Twice Daily	14	Yes	Yes	Dhx-PODs
Domperidone (PO) tablets	10mg	3 X Per Day	14	Yes	Yes	Dhx-PODs
Ranitidine (PO) tablets	75mg	Twice Daily	14	Yes	Yes	Dhx Relabel on ward- GP please note the dose of RANITIDINE is 75mg BD and not 150mg BD- please amend this on repeat Px.Thx- [redacted]
AquADEKS Chewable Tablets (PO)	one tablet	Twice Daily	14	Yes	Yes	DHx-OSD -ward
Montelukast (PO) chewtablets	5mg	Evening	14	Yes	Yes	Dhx-PODs
Acetylcysteine 200mg tablets (PO)	400mg	Twice Daily	14	Yes	Yes	Dhs-OSD
Slow sodium 600mg tablets (PO)	2 tablets	Twice Daily	14	Yes	Yes	Dhx-OSD
Cetirizine (PO) tablets	5mg	Twice Daily	14	Yes	Yes	Dhs-PODs
Creon 10, 000 (PO) capsules	as needed	When Required	14	Yes	Yes	Dhx-PODs

TTA: To take away (medication patient needs to take home on discharge).
Figure 3.5. CRS®TTA transcription to document for patient

4. Summary Care Records (SCR, from NHS digital[146]): this is the information of primary care electronic prescribing. This document was used for the prospective study. Due to lack of permission there is no example of the medication listed of a patient on SCR.
5. Patient's own drugs (PODs): this is the physical medication the patient brings to hospital that is checked by pharmacy staff to confirm reconciliation on admission. In the UK, by law all medicines categorised as "Prescription Only Medicines" (POM) must have a label identifying the name of the patient, drug

dispensed and instructions on how to take these medicines. Figure 3.6 is an example of the labelling system used in the UK prescribed medicine.



Note the square D and C for dispenser and checker to sign the label attached to drug.

Figure 3.6. Example of type of label used in the UK.

6. Drug chart of the patient: this was used in the prospective study. The drug chart is the tool used in the wards to prescribe and record administration of medicines. It is an A4 booklet different number of pages with different sections for prescribing and recording administration. Figures 1.2-1.7 in introduction chapter correspond to different pages of a drug chart.
7. Homecare prescriptions: managed in secondary care by specialist teams. In 2015, High cost nebulisers (HCN) commissioning changed and the patients on HCN needed repatriating to secondary care. HCN are currently commissioned by NHS-England whereas the previous commissioner was primary care via clinical commissioning groups (CCG). At the RLH this was done via homecare[63] during 2014. The homecare prescriptions used for Paediatric CF patients at Barts Health have been agreed and

developed by the Consultant Pharmacist with the homecare company as a proforma to aid mitigating prescribing errors. Figure 3.7 is an example of the prescription used at the Royal London Hospital. The medications included in homecare for CF children relate to either HCN or Ivacaftor. These prescriptions are another source of information that should be used to confirm drug history for medicines reconciliation when patient comes into hospital.

DETAILS OF PRESCRIBED DRUGS *(please tick appropriate box)*

Drug	Dose & frequency	Continuous	Alternate months	Route	Quantity per month/alternate month
Aztreonam (Cayston®) 75 mg	Inhale ONE vial THREE times a day (at least 4 hours apart) as directed		☐	Nebulised	84 vials (total 1 box containing 84 vials or Aztreonam, diluent plus 1 nebuliser headset)
Colistin (Colomycin®) 1 million IU	Reconstitute ONE vial and nebulise twice daily as directed	☐		Nebulised	60 vials (total 6 boxes – each box containing 10 vials)
Colistin (Colomycin®) 2 million IU	Reconstitute ONE vial and nebulise twice daily as directed	☐		Nebulised	60 vials (total 6 boxes – each box containing 10 vials)
Colistin (Promixin) powder for nebulisation® 1 million IU	Reconstitute ONE vial twice daily and nebulise as directed via I-Neb	☐		Nebulised	60 vials (total 2 boxes – each vial is 1 megaunit in strength)
Colistin (Promixin) powder for nebulisation® 1 million IU	Reconstitute ONE vial and nebulise HALF of this vial twice daily. Discard contents of unused vial and prepare a new one for each administration	☐		Nebulised	60 vials (total 2 boxes – each vial is 1 megaunit in strength)
Colobreathe®	Inhale the contents of ONE capsule (1.6625 MIU) using the Colobreathe Inhaler twice a day as directed	☐		Inhaled	56 capsules (total 1 box containing 56 capsules)
Dornase alfa (Pulmozyme®) 2,500iu/2.5ml	Inhale ONE nebule once daily as directed	☐		Nebulised	30 Nebules (Total 1 box)
Dornase alfa (Pulmozyme®) 2,500iu/2.5ml	Inhale ONE nebule twice daily as directed	☐		Nebulised	60 Nebules (Total 2 boxes)
Mannitol (Bronchitol®) 40mg	Inhale the contents of TEN capsules (400mg) twice daily as directed	☐		Inhaled	560 capsules (Total 2 boxes – each box containing 280 capsules and 2 inhalers)
Kalydeco (ivacaftor) 150mg tablet	Take ONE tablet TWICE a day	☐		Oral	56 tablets (4 weeks)
Kalydeco (ivacaftor) 150mg tablet	Take ONE tablet daily	☐		Oral	56 tablets (8 weeks)
Kalydeco (ivacaftor) 150mg tablet	Take ONE tablet TWICE a week	☐		Oral	56 tablets **(supplied every 7 months)**
Tobramycin (TOBI®) 300mg/5ml	Inhale ONE Nebule twice a day (not less than 6 hours between doses) as directed		☐	Nebulised	56 nebules (total 1 box containing 56 nebules)
Tobramycin (TOBI®) 28mg Podhaler	Inhale the contents of FOUR capsules twice a day as directed		☐	Inhaled	224 capsule (total 1 box containing 224 capsules and 5 inhalers)
Tobramycin (BRAMITOB®) 300mg/4ml	Inhale ONE Nebule twice a day as directed		☐	Nebulised	56 nebules (total 1 box containing 56 nebules) ☐ 6 month LC Plus Neb Set ☐ 6 month Filter Valve Set
Water for injections 5ml	2-4 ml To be used to reconstitute Colistin twice daily as directed by the CF team	☐		To reconstitute Colistin	60 plastic ampoules
Sodium Chloride 0.9% 5ml	2-4 ml To be used to reconstitute Colistin twice daily as directed by the CF team	☐		To reconstitute Colistin	60 plastic ampoules
Plastic Syringe 5ml	To be used if required to reconstitute Colistin as directed by CF team	☐		To reconstitute Colistin	6 packs of 10 x 5ml

Allergies

Additional comments
dispense monthly
dispense alternative months
months prescription
please deliver 2 months supply at each delivery

Figure 3.7. Homecare proforma used for CF patients on HCN.

In summary, the next Table (Table 3.1) shows the description of the purpose of the information used in each phase of the study.

Table 3.1. Summary of sources of information used with main peculiarities of the system related with pharmacy.

	Sources of information	**Purpose**
Retrospective phase	Electronic Prescribing Record (EPR)	Discharge electronic prescription (TTA*), given to parents on the same day at discharge. Sent to Primary care. Validated by pharmacist.
	Discharge letter (DL)	Comprehensive document that includes clinic history of patient such as microbiology results, spirometries and list of drugs prescribed on discharge. Sent to parents' although not necessarily same day of discharge. Sent to Primary care. Not validated by pharmacist.
Prospective phase	Clinical Record System (CRS)	Database with discharge electronic prescriptions or TTA* including all sort of health related documents (equivalent to EPR in the retrospective study). Validated by pharmacist.
	Sumary Care Records	Primary Care prescriptions records of acute and repeat prescriptions. Not validated by pharmacist.
	Patients own drugs (PODs)	Physical medication of the patients, labelled. Used in reconciliation of medicines in hospital admission. Validated by community pharmacist
	Drug chart of the patient	Hand written prescription used on the wards that records administration of medicines. Validated by ward pharmacist.
	Homecare prescriptions	Prescriptions from specialist in secondary care Used in reconciliation of medicines in hospital admission. Validated by pharmacist.

* TTAs (to take away, related to medication at discharge for the patient) are named in this study EPR for the retrospective study and CRS for the prospective study. TTAs are created with a section for pharmacist validation.

3.4. Patients.

At present the Respiratory Department looks after CF children of East of London, West and North East Essex. RLH also share-cares with Colchester and Queens Hospital. The Specialist Clinical Nurses for CF have a database of the patients that are being looked after by the department.

The specialist nurse notified patients in the quarterly CF bulletin that a project would be carried out by Pharmacy department and should any patient not wish to be added to the project to let her know.

3.4.1. Retrospective phase.

All paediatric CF patients admitted to RLH to receive IV antibiotics during the years of 2013 and 2014 were included in this period of the study.

A list of CF children registered in the database of 2013 and 2014 period was provided by the specialist nurse.

Each hospital number was entered in the electronic prescribing system (EPR) in order to establish if the patient had been admitted into hospital during any of the two years of the retrospective stage.

When the patient was identified in the system, this was registered in the database to follow the study and data started to be collected.

3.4.2. Prospective phase.

The patients included in the prospective phase of the study were all CF patients admitted into the respiratory ward (7E ward) to receive IV antibiotics in the RLH from May 2016 to December 2016 (8 months).

The Paediatric respiratory pharmacist covering 7E ward and the Pharmacy Technician based on the wards were informing of any new CF patients that were admitted. The name and the room of the child were identified with the daily handover list that is kept in the ward. The patient's notes and drug chart were taken to do a full drug history of the patient.

A data collection form was designed and this corresponds to the next Figure 3.8. Once data was collected, the non-confidential information was entered in an excel database. These sheets were kept locked for confidential information protection and will be destroyed after presenting the study to the team.

Name/Sex DOB MRN-NHS
Age at discharge Social: Parent's English 1st language Y/N; living with both parents same house Y/N; Lives in: renting/own/social housing/other
Associated pathologies 1. Panc insufficiency; 2. GORD; 3. Diabetes; 4. Asthma; 5. Gallstones/Liver disease; 6. Other (specify)
Other:

ADMISSION Date of admission Reason for admission: **1.** Elective IV; **2.** Elective preprocedure; **3.** Infective exacerbation
Number of medication patient is regularly on previous admission (this number should match with primary care data)
Discrepancies of prescription with regular medication on admission Y/N Number of med errors on admission Are these med error 1. Justified or 2.No Justified
If no justified med error=Admission Conciliation error (ACE)- Categories:
0-1 Drug omitted/continued without need ; **R-1.** Wrong drug; **0-2** Omitted dose; **R-2** Wrong dose; **O-3. Omitted** frequency; **R-3.** Wrong frequency route; **0-4.** Omitted duration; **R-4** Wrong duration; **0-5.** Omitted Pharm form; **R-5** Wrong Pharm form; **0-6.** Omitted route; **R-6** Wrong route; **7.** Other
Non medical errors: **1.** Allergies not filled in; **2.** Prescription not signed; **3.** Other (state)
Gravity : **1.**no harm; **2.** medium harm (needed hourly observations); **3.** serious harm (needed extra hospital attention, length stay)
Potential gravity: **1.**no harm; **2.** medium harm (needed hourly observations); **3.** serious harm (needed extra hospital attention, length stay)
Intervention accepted **Y/N** **Cause: Educational/Organizational/Technological/Human/Communication/Other:…**

Primary care check- consent given Y/N
Same allergies as admission **Y/N**- or need update due to new allergy identified if yes- to follow at discharge with note for GP on TTA- see **
Number of medicines on repeat prescription (do not count lancets, non medical products)
Number of meds needed to be added to repeat Px and this needs to be followed on TTA at discharge in communication (see **)
Number of discrepancies on repeat Px vs how patient takes/should take Are they Justified discrepancies **1.**Yes **2.** No Justified discrepancies-(Error in primary care)
Categories:
0-1 Drug omitted/continued without need ; **R-1.** Wrong drug; **0-2** Omitted dose; **R-2** Wrong dose; **O-3. Omitted** frequency; **R-3.** Wrong frequency route; **0-4.** Omitted duration; **R-4** Wrong duration; **0-5.** Omitted Pharm form; **R-5** Wrong Pharm form; **0-6.** Omitted route; **R-6** Wrong route; **7.** Other
Prompt card added to drug chart for discharge alert **Y/N**
Ward pharmacist fully informed of discrepancies to add to discharge **Y/N** **Cause: Educational/Organizational/Technological/Human/Communication/Other:…**

DURING STAY- Number of regular medication being modified during admission:
Number of interventions/pharmacist actuations identified during stay Accepted **Y/N**
Type interv: 1/ 2/ 3. **1. Preventive:** signature, weight, allergies, monitoring needed, other
2. Corrective: drug, dose, frequency, pharm form, duration, route.
3. Educational: doctor, nurse, patient/relative
Will GP need to be inform for any of above amendments? **Y/N** (then for discharge communication- see **)

DISCHARGE Date of Discharge/Day of the week Number of days in hospital weight written in TTA **1.** Yes, **2.** No
****Have the modifications being notified to primary care at discharge (Information for GP to update) Y/N/Not applicable
Prescription written by **1**. Junior Doctor (ST1-ST3), **2.** Senior(ST4 mid rota-ST8/fellow), **3.** Pharmacy (DADL); **4.** Not written or incomplete (missing more than 5 drugs)
Prescription validated by **1.** Junior (B6), **2**. B7 (Specialist in Resp- if junior B7 consider B6 or 8a and above) **3.** Not validated
Number of medication prescribed on discharge Number of medicines Px as brand name:
Any discrepancies noted during revalidation **Y/N** If yes-Number of discrepancies Are these **1.** justified discrepancies or **2.** Non-Justified (=validation errors)
0-1 Drug omitted/continued without need ; **R-1.** Wrong drug; **0-2** Omitted dose; **R-2** Wrong dose; **O-3. Omitted** frequency; **R-3.** Wrong frequency route; **0-4.** Omitted duration; **R-4** Wrong duration; **0-5.** Omitted Pharm form; **R-5** Wrong Pharm form; **0-6.** Omitted route; **R-6** Wrong route; **7.** Other
Non medical errors: **1.** Allergies not filled in; **2.** Prescription not signed; **3.** Other (state)
Gravity **1. 2. 3.**
Correct dose/frequency **Y/N-** lipoph vitamins Px **Y/N-** Creon Px **Y/N-** Clear Px **Y/N-** Interactions free **Y/N-** Allergies documented **Y/N**
Informed Team to query **Y/N** **Cause: Educational/Organizational/Technological/Human/Communication/Other:…**

Figure 3.8. Data collection form used during the prospective study.

3.5. Variables studied.

The number of variables analysed has been high. To facilitate the comprehension of the study Table 3.2 summarises the variables studied in both retrospective and prospective phases and the main source of information used.

Figure 3.9 represents in a diagram the steps of how the study was followed and implemented, and in bolded letters the sources used to detect improvement opportunities projecting towards an improved discharge prescription with correct medication prescribed.

Table 3.2. Summary of variables in each phase of the retrospective and prospective study with source of information used

Variables studied		Retrospective		Prospective			
		Discharge		Admission (DHx Reconciliation)		Hospital stay	Discharge
		Electronic prescribing (EPR)	Discharge letter (DL)	Drug chart	Primary care (SCR)	Drug chart (Green pen)	CRS (electronic discharge)
Related to patient	0- Hospital number	✓	✓	✓	✓	✓	✓
	1- Age	✓		✓			
	2- Gender	✓		✓			
	3- Number associated pathologies	✓					✓
	4- Type associated pathologies	✓		✓			
	5- Parent's English			✓			
	6- Child living with parents			✓			
Related to hospital stay	7- Reason for admission	✓	✓	✓			
	8- Days of hospitalisation (n)	✓		✓			✓
	9- Week day of admission			✓			
	10- Week day of discharge	✓					✓
Related to drug therapy	11- Weight	✓	✓	✓	✓		✓
	12- Allergy documentation	✓	✓	✓	✓	✓	✓
	13- Same allergies in PC				✓		
	14- Type of drugs	✓	✓			✓	✓
	15- Prescribing doctor	✓	✓				✓

	16- Validating pharmacist	✓					✓
	17- Seniority of the pharmacist	✓					✓
	18- Presence of DL		✓				
	19- Date of DL		✓				
	20- N discrepancies in DL versus EPR		✓				
	21- Drugs prescribed (N)	✓	✓	✓	✓	✓	✓
	22- Brand name drugs (N)	✓					
	23- High cost nebulisers in PC				✓		
Related to Improve-ment strategies	24- Deeper MR (≥3 sources)			✓	✓		
	25- N prompt cards effectuated			✓			
	26- Pharm intervention n and type					✓	
	27- Pharm intervention accepted					✓	
	28- N discharges drug listed						✓
	29- Communication needed				✓		
	30- Communication done						✓

N=Number of; DHx: Drug history; MR=Medicines Reconciliation; PC= Primary Care; Px= Prescription; H= Hospital.

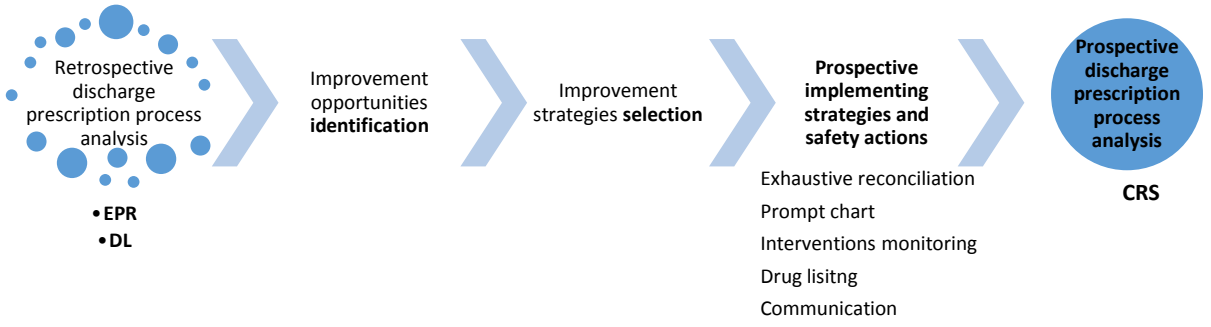


Figure 3.9. Diagram of the process of the ambispective study followed

3.5.1. Patient related variables.

The following variables relating to patients were collected from the hospital number and electronic prescribing. Variables of age, gender, hospital number and associated pathologies were studied in the clinical part of the document in EPR and in the discharge letter. Socio-demographic variables 5 and 6 were collected from information directly from the clinical specialist nurses.

0. Hospital number: variable collected to study other variables kept in different database. Given nil number as this was used but not presented for any of the results.
1. Age of the patient on the day of discharge: quantitative continue variable. This variable was collected in years.
2. The gender of the child: qualitative dichotomy variable that takes values boy (male)/ girl (female).
3. Number of associated pathologies: cumulative continue variable that sums the number of associated pathologies of a child with CF presented at the time of discharge.
4. Associated pathologies of the patient: categorical variable that takes into account the number and type of associated pathologies the child has as they are related to CF. These pathologies are well known within CF patients are they were categorised the following way:
    - Pancreatic insufficiency
    - Gastro-oesophagus reflux disease (GORD)

- Diabetes
- Liver disease
- Other (ABPA, DIOS, bronchiectasis, asthma, …)

5. Parent's English: Variable related to the first language of the parents. It is a qualitative dichotomy variable that takes values **yes** when the English language of mum/dad/carer is their first mother tongue or **no** when English is an additional language.
6. Parental support: categorical variable that refers to the child living with one parent (mother or father, including foster parents) in the main home or with both parents (mum and dad).

3.5.2. Hospital stay related variables.

These variables were obtained from EPR and DL for each patient's during the retrospective part or from the drug chart and electronic discharge prescription (CRS) in the prospective phase of the study.

7. Reason for admission: qualitative dichotomy variable that takes values of elective admission or infective exacerbation (severe admission). These can be:
    a. Elective admission: this type of admission is for patients that come in to hospital either
        - to be admitted for routine intravenous (IV) treatment every 3 months due to their clinical condition, or
        - Pre-procedure admission: this includes patients that are admitted for a procedure like gastrostomy, ear/nose and throat surgery, bronchoscopy, etc. They are admitted few

days prior to procedure and discharged few days after in order to receive IV antibiotics

b. Infective exacerbation: this includes different situations listed below:
   - Severe clinical symptoms or deteriorated lung function.
   - Mild to moderate clinical symptoms or reduced lung function that are not improving with oral antibiotics.
   - Eradication needed of isolated microorganism/s.

8. Number of days the patient stayed in hospital during that admission: quantitative continue variable calculated as the difference of days between the date of admission and the discharge date.
9. Admission day of the week: categorical dichotomy variable defined as the type of service provided by pharmacy service during the week. This variable was collected in the prospective study.
   a. Monday- Friday: during these days a ward pharmacist cover is arranged and respiratory doctor in on duty. A pharmacist is ward based or reachable between 9am-5pm.
   b. Saturday-Sunday: during these days there is no pharmacist ward cover and the doctor on duty is not necessarily a respiratory doctor. The on call pharmacist is reachable but has not necessarily had any paediatric experience or covered any respiratory ward before.

10. Discharge day of the week: as above, this was a categorical dichotomy variable defined as the type of service provided by pharmacy service during the week.

3.5.3. Drug therapy related variables.

As pharmacists are integrated in the multidisciplinary team with daily ward rounds, continued pharmaceutical assistance during hospital stay was studied in the best possible way in order to provide quality of the discharge prescription. Hence variables were collected in three different steps: admission of the child, hospital stay and at discharge.

The variables in this section 3.5.3 relate to either primary care prescriptions, admission medicines, hospital stay or at discharge in either the retrospective study or prospective or collected for both studies.

The discharge date was estimated from the prompt card attached to the drug chart during the admission data collection and a note was taken in the diary in order to capture the information during stay and analyse the discharge prescription on CRS. As confirmation of the date of discharge, the pharmacist covering 7E ward was informing the investigator of the potential CF children going home on the day.

The variables studied that relate to drug therapy were the following:

11. Related to child's weight being recorded (dichotomy categorical):
    i. Yes: if the weight had been recorded.
    ii. No: when the weight was not recorded.
12. Related to the allergy section (dichotomy categorical):

i. Yes: if the allergy section had been documented.
ii. No: if the allergy section had not been documented.

13. Same allergies documented in primary care as in hospital (dichotomy categorical):
    i. Yes: If the allergies stated in primary care records were the same as in CRS.
    ii. No: if there were any allergies documented different than in CRS.
14. Related to type of medication commonly used in CF in the UK: these variables were studied in groups of drugs that were considered the most common regular medication in a child with CF treated in the UK. They were studied during the retrospective and prospective studies in discharge prescriptions (also on admission prospectively) and were dichotomy categorical variables.
    a. Nebulised mucolytic prescribed:
        i. Yes: if at least one nebulised mucolytic was prescribed.
        ii. No: if the prescription did not have any nebulised mucolytic.
    b. Motility, anti-reflux, proton pump inhibitor (PPI) or any gastrointestinal tract drugs prescribed:
        i. Yes: if there was at least one drug prescribed for the gastrointestinal tract.
        ii. No: if there was no gastrointestinal medication in the prescription.
    c. Pancreatinin prescribed in pancreatic insufficient patients:

i. Yes: if any pancreatinin enzymes drugs were prescribed.
ii. No: if the prescription had non pancreatinin enzymes.

d. Lipophilic vitamins prescribed in pancreatic insufficient patients:
   i. Yes: if there were any lipophilic vitamins in the prescription.
   ii. No: if there were no lipophilic vitamins prescribed.

e. Nebulised antibiotics prescribed:
   i. Yes: if at least one nebulised antibiotic was prescribed.
   ii. No: if the prescription did not have any antibiotic nebulised.

f. Oral or IV antibiotics prescribed:
   i. Yes: if any oral or IV antibiotic was prescribed.
   ii. No: if no antibiotic was prescribed.

g. Inhalers prescribed: this variable was studied as salbutamol inhalers were constantly seen prescribed in CF children, although these are not considered always indispensable in CF:
   i. Yes: if there was at least one inhaler prescribed.
   ii. No: if the prescription did not have any inhalers.

15. Prescribing doctor for discharge electronic prescription: qualitative categorical variable defined as the title of the doctor that writes the electronic prescription for that episode.
   i. Junior doctor (equivalent to a Resident 1-3 in Spain).
   ii. Senior doctor/Registrar/Clinical Fellow (equivalent to a Resident of year 4-5 in Spain).

iii. Consultant (equivalent to the specialist doctor or *medico adjunto* in Spain).

16. Related to the pharmacist that validated the medication prescribed/listed on discharge, dichotomy categorical variable:
    i. Yes: if the pharmacist had validated the medication.
    ii. No: if the pharmacist had not validated the medication.
17. Related to the seniority of the pharmacist validating the discharge prescription, dichotomy categorical variable. When junior pharmacists were validating the prescription or the validation was performed by a senior pharmacist (Band 7 who had been working over 6 months as a B7 within the paediatric pharmacy department).

    Below variables 18-19 were referred as administrative analysis of the DL.

18. Related to the presence discharge letter (DL) on discharge. This was studied in the retrospective phase, and also was a dichotomy categorical variable.
    i. Yes: if the patient had DL.
    ii. No: if the patient had no DL for that admission.
19. Date of discharge letter. This variable was calculated with the difference of days between the date of the DL and the date of the day of discharge stated in the same discharge letter. The variable of date of DL would give an indicator of delay of DL and it was studied in the retrospective study.

20. Number of discrepancies found in DL compared with the EPR used as a reference.
21. Number of drugs prescribed (cumulative continue variable): this is the total number of medicines that were prescribed per patient in the retrospective phase in EPR and DL. In the prospective phase this variable was collected from four information sources: the drug chart on and after admission, the repeat prescription in primary care and the discharge prescription on CRS.
22. Number of drugs that had been prescribed as brand name per patient (cumulative continue variable). This variable was studied in EPR as indicative of using correct brand names for CF disease.
23. Existence of high cost nebulisers (HCN) in the repeat prescription. This variable looked at the presence of any of the high cost nebulisers that had been repatriated to secondary care during 2014-2015 taking values of yes/no (dichotomy categorical variable). This variable showed a potential cost lost or misuse of the drug if general practitioner continued prescribing these HCN (ig. Bramitob®, Dornase alpha, Colistin®/Promixin®…).

3.5.4. Improvement strategies and safety actions variables.

The following variables were collected prospectively because they were defined and implemented in the best capacity level as a consequence of the results of the retrospective study.

24. Medicines reconciliation: categoric variable (yes or not) that regarded whether the pharmacist had done a medication

reconciliation with the patient's regular medication within the first three days of admission with a minimum of 3 sources of information.

25. Number of drug charts with attached prompt chart: cumulative continue variable that was defined to improve the prescription process at discharge. The aim of the prompt card was to avoid common mistakes found in the retrospective study or possible errors identified with the new computer system used.
26. Pharmacy interventions during the hospitalisation of the patient: cumulative variable that defined the number of interventions made by any pharmacist during the time the patient was admitted and up to the discharge day that were reflected in the drug chart. This variable was captured by checking any contributions to care made by using green pen on the drug chart (green pen is the colour used by pharmacist). For capacity reasons, verbal interventions during ward round or whilst pharmacist was in the ward were not captured. The classifications used in these contributions to care were:
    a. **Preventive interventions** (non-medication errors):
        1. Lack of signature after prescribing.
        2. Weight omitted on the drug chart.
        3. Allergies not confirmed prior to prescribing.
        4. Illegible prescription or drug monitoring plan.
    b. **Corrective interventions** (medication errors), classified depending on the pharmacotherapy recommendation:

1. Omit or add regular drugs to treatment.
2. Amend dose.
3. Amend frequency.
4. Specify/amend length of treatment not specified.
5. Amend pharmaceutical form.
6. Specify/amend route of administration not specified.

c. **Educational interventions** for the professional prescriber, nurse or patient/relative. These include information on how to administer a drug given by nasogastric (NG) route or percutaneous endoscopic gastrostomy (PEG) route or oral medication that needed dose adjustment in an off license use of tablets such as crushing and dispersing tablets information, and volume required for specific pharmaceutical form, timing of drug administration, potential side effects monitoring.

27. Pharmacist interventions or contributions to care accepted: this was a dichotomy categorical variable studied per hospital admission of each patient finding if the intervention had been accepted (yes) or not (no).
28. Number of discharge prescriptions in which the pharmacy technician or pharmacist had previously drug listed patient's regular medication on the electronic system (cumulative continue variable). This task was introduced a few weeks after the commencing period of the prospective study in order to help in

different ways: getting discharge medication on time; helping speed up the discharge process; as well as avoiding omitted prescribing mistakes in the recently new electronic discharge system implemented (CRS). This service was not always facilitated as it depended on the capacity of the paediatric pharmacy department.

29. Communication needed with primary care (dichotomy categorical variable): If there was information that would need to be addressed to the general practitioner to update the most recent medication records (referring to the information collected during admission in medicines reconciliation and during hospital stay if there were any changes of pharmacotherapy too).
    i. Yes: when either justified discrepancies had been found or regular medication of the patient had been amended.
    ii. No: when no changes occurred of patient's regular medication so no need to emphasise anything at primary care level.
30. Communication provided to primary care on discharge (when needed) (dichotomy categorical variable):
    i. Yes: when any amendments needed were addressed to the general practitioner and documented in the electronic prescription.
    ii. No: when all amendments needed were not addressed to the general practitioner and therefore not documented in the electronic prescription.

3.6. Improvement opportunities.

Improvement opportunities (I.O) were defined as any circumstances that cause or could cause a medication error to reach or harm a patient due to lack of information or incorrect information in the prescribing process[147].

I.O were studied in the retrospective and prospective study.

- In the retrospective phase the I.O were analysed in **EPR** as well as in the **DL**, using EPR as a reference to conciliate the information written in the DL.
- In the prospective phase the I.O were analysed:
    - On admission within the first three days of admission, evaluating discrepancies and conciliation errors comparing the primary care repeat prescription and the drug chart (as part of the improvement and safety actions with an exhaustive or deeper medicines reconciliation than the standard one). These are presented in the results chapter as part of the implemented improvement strategies and safety actions, separated from the improvement opportunities section.
    - At discharge the prescriptions were reviewed after validation up to the next 3 days after patient's discharge, comparing the prompt card and the drug chart with **CRS** (electronic prescription at discharge) system after pharmacist validation.

3.6.1. Improvement opportunities classification.

The channelled actions to prevent or solve the errors found in the retrospective phase during the quality evaluation of the discharge prescriptions and also during medicines reconciliation studied prospectively were initially classified in two types:

a. Non-medication errors such as lack of signature in prescribing, allergies not confirmed prior to prescribing, omitted weight or hand written prescription illegible. At discharge lack of signature was not considered since prescriptions were made in electronic system. However, all non-medications errors indicated above were analysed during the admission and hospital stay in the prospective study. They were considered first steps to provide a neat discharge prescription with no queries to follow whilst and after prescribing at discharge.
b. Prescription errors: defined as medication errors and classified in the next section 3.7.

3.7. Medication errors.

Medication errors (ME) were defined as any preventable incident that could cause harm to a patient for inappropriate use of the drugs due to incorrect/unclear prescription, during hospital stay or at home[148].

3.7.1. Classification.

The type of ME errors followed the next classification when any of the following parameters *(6 rights)* that were considered mandatory in paediatric prescriptions had any unintentional mistake:

1. Drug.
2. Dose.
3. Frequency.
4. Duration.
5. Pharmaceutical form.
6. Route of administration.

And all above factors were studied for any of the following subtypes:

- *Committed errors:* defined as an actual mistake in the prescription due to lapse, lack of knowledge, lack of procedures, unawareness of procedures or guidelines, training need, technological causes, etc.
- *Omitted errors or missing errors:* defined as any omission of essential information included in Table 3.3 on EPR or the discharge letter.

The following Table 3.3 describes the definition of type and subtype of the medication errors.

Table 3.3. Definition of the type and subtype classification of the medication/prescribing errors

	Committed: incorrect information in the actual prescription	**Omitted:** lack of completion of the prescription
Drug	When the drug prescribed was either: • Wrong for the indication needed; • Continued when should have been stopped; • Interactions/absorption problems affecting efficacy or causing potential medication related problems (itraconazol and proton pump inhibitors prescribed together, for instance).	• When the name of the drug was missing in the list of medication in EPR but was listed in the list of medication in the discharge letter or viceversa; • When the drug that the patient was regularly on had been missed during admission/discharge. Examples: nebulised mucolytics/antibiotics, insulin, voriconazole, etc • When there was evidence that rescue antibiotics should be easily accessible to patients in primary care and these were not listed on the repeat prescription. Examples: Co-amoxiclav, Ciprofloxacin …
Dose	• When the dose was prescribed in volume or wrong units (excluded AquADEKs®, Sytron® and Lactulose). • When either higher than or less than 20% of the dose for age/weight was prescribed. This was checked with age/weight of the child and CF dosing guidelines used locally or British National Formulary (BNF) for children in the medication listed.	• Dose or units missing in the prescription. • Dose stating "take as directed" (excluded pancreatinin enzyme preparations and creams/ointments or medication that was not related to CF or any associated pathology)
Frequency	• Any frequency higher than or less than 20% of what would be expected for that age/weight from the references used were considered mistakes.	• Incomplete frequency or omitted in the prescription (saying "when required" with no maximum number of times per day).

Duration	When the duration prescribed for a drug was incorrect and evidence to show that this was wrong was found.	Considered for: • Antibiotics; • Steroids; • Alternating nebulised treatments; • New medication prescribed (if there was any review date to prompt doctors to check this in the following visit/admission).
Pharma-ceutical form*	• Wrong pharmaceutical form prescribed; • Better preparation for adherence was available with minimal cost implications; • Less expensive pharmaceutical form available in the market; • Inconsistent pharmaceutical forms in the same prescription for other drugs; • Evidence that patient already taking tablets but liquid preparations were being issued (exception itraconazole liquid).	• When more than one presentation was licensed in the market (referring mainly to liquid preparations) if the pharmaceutical form was not present in the prescription it was considered and improvement opportunity. • The type of nebuliser/inhaler/insulin prescribed was missing.
Route of administra tion*	• Wrong; • Inconsistent with other medicines that would normally be administered in the same route.	• Missing in the drug.
*Note that Pharmaceutical form and Route of Administration were mandatory factors for prescribing whilst using EPR© system, whilst CRS© system would allow prescribing without this information.		

3.7.2. Identification.

Medication errors (ME) in the **retrospective phase** of the study were identified by observing EPR and then comparing the discharge letter (DL) with EPR in each patient's discharge. The doses and frequencies were calculated according to CF guidelines and latest weight/age found either on EPR or DL.

The DL contained a medication section which was not validated by the pharmacist. This section was compared to the EPR that is normally validated by the pharmacist prior to discharge, considering EPR was the latest new medication regimen the patient was prescribed on the actual day of discharge.

Medication errors in the **prospective phase** of the study were detected the same way as in point 3.6 for I.O:

- On admission: during drug history medicines reconciliation with primary care prescription, drug chart and patient's own medication.
- At discharge: after pharmacist validation with CRS compared with drug chart and information written on the prompt chart.

The evaluation of medicines reconciliation is explained in section 3.8.

During hospital stay no ME were analysed but the types of interventions that were done by pharmacist on the ward with the green pen on the drug chart as part of the improvement strategies and safety actions

implemented after the retrospective study (see variables number 26 and 27).

3.7.3. Causes.

Although most errors may have multiple causes, the main cause contributing to the error was selected. The classification was categorised by the investigator when reviewing the errors, and the main circumstances in which the error occurred were evaluated depending on: the type of error, the member of staff involved, the moment and the time/day, the type of prescribing system used. This classification was made purely subjectively, however the investigator was in all cases the same person evaluating the cause of error in both parts of this study: retrospective and prospective. The causes of the prescription errors were classified in the following Table 3.4.

Table 3.4. Main causes of ME and some examples that can contribute to the cause.

Cause	Examples
Technological	• Computer system that does not transfer information properly into final document like signature, allergy or weight; • Mandatory prescribing of 6 rights not set up on computer system; • Computer system being down. • Lack of safety alerts on computer system (maximum dose, allergies when prescribed a drug that contains the allergenic ingredient, drug interactions...)

Organisational	• Guidelines not easily available. • Overload work, shortage of staff. • Weekend service admissions/discharges (no respiratory team and minimal pharmacy service). • Locum healthcare professionals not knowing the patient/condition or the importance of updating records on time.
Communication	• Lack of communication between healthcare professionals or between patients and healthcare professionals. • Language barrier.
Educational	• Lack of knowledge of the mistake that could be prevented by providing training. • Lack of knowledge of special procedures for prescribing expensive/restricted drugs.
Human	• Awareness of the correct way of prescribing but unintentionally mistake occurred due to lapse, forget, distraction.

3.7.4. Severity.

The severity of medication errors was categorised depending on the potential pharmacotherapy morbidity, as per IASER© method, which is a scale from 1 to 5 that describes higher severity while going up the values[149]. The following Table 3.5 defines de severity scale.

Table 3.5. Scale to evaluate the potential severity of the medication errors (IASER® method).

Grade	Description
1	ME that has not caused any harm or that the harm caused was reversible (with no changes in vital signs) but monitoring was required.
2	ME that has caused reversible harm (with no changes in vital signs) but modification of treatment was required.

3	ME that has caused reversible harm and required additional treatment, prolonged hospital stay.
4	ME that has caused irreversible harm or disability.
5	ME that caused patient's death.

ME: Medication error

3.8. Medicines reconciliation evaluation.

Medication reconciliation is a formal process of obtaining and verifying a complete and accurate list of each patient's current medicines. It is an essential process for patient safety, promoting safer use of medicines with effective communication at the interface, particularly when patients are admitted and discharged from hospital[150].

In the **retrospective phase,** DL was reconciled with EPR as this was the only source of information available.

However, medicines reconciliation evaluation was studied prospectively during transition of patient's care as explained in point 3.6.

The necessary data to elaborate the drug history (or medicines reconciliation on admission) was obtained from a minimum of three sources selected from the following:

- patient's own medicines (PODs);
- information from the parents;
- primary care records (SCR);
- previous admission's discharge prescription;
- latest medication list written down in clinic;

- homecare prescription when the patient was on regular high cost nebulisers such as *Dornase alpha* or nebulised antibiotics.

The NHS number was needed to access primary care records and permission was granted beforehand.

The evaluation was made depending on:

1. Discrepancies:
    i. Yes:
        - When the information in the primary care prescription did not match with the final pharmacotherapy history taken.
        - When the information in the drug chart during admission containing patient's regular medication (excluding nebulised antibiotics) did not match the pharmacotherapy history taken.
    ii. No:
        - When the same medication with same dose and frequency the patient was regularly on was prescribed in the repeat prescription in primary care.
        - When the same medication with same dose and frequency the patient was regularly on, was prescribed in the drug chart.
2. If the discrepancies found were justified or non-justified:
    i. Justified discrepancies were those discrepancies that had been intentionally changed by the prescribing doctor in order to optimise dose or treat according to current clinical status of the patient, for example.

ii. Non justified discrepancies were considered as conciliation errors which were prescribing errors occurring during transition of care.

If the discrepancy was justified, it was excluded as medication error. If the discrepancy was not justified, it was included as reconciliation error.

3. Number of medication errors during reconciliation found per patient.
4. Classification (type and subtypes), cause and severity of the medication errors during reconciliation corresponds to the same one listed in Section 3.7.1.

3.9. Safety actions and improvement strategies.

From the results obtained in the retrospective phase the following improvement measures for the quality of the prescribing at discharge were implemented for evaluation in the prospective study.

3.9.1. Print screen of the validated discharge prescription.

In order to help minimise medication errors in the DL as well as discrepancies between DL and the electronic prescription -commonly named TTA (to take away)-, it was agreed that the DL would contain the same information as the electronic prescription. Therefore, the prescription section in the discharge prescription in CRS (normally validated) would be print screened and this information would be pasted in the word document of the DL. In this case DL would not need to be followed up prospectively, since it would have the same information as in

CRS. But also there would be consistency in information given to patients and primary care doctors for the same episode.

3.9.2. In depth medicines reconciliation on admission.

Drug history reconciliation was carried out within the first 24 hours as per standard policy of reconciliation, however an exhaustive or deeper drug history using a minimum of three sources of information was performed during the first 72 hours of the patient's admission. Out of these three sources of information one of them had to be primary care repeat prescription (if consent was granted) and another one had to be homecare prescription (if patient was on HCN at home). Any discrepancies were followed up during hospital stay to avoid discrepancies at discharge.

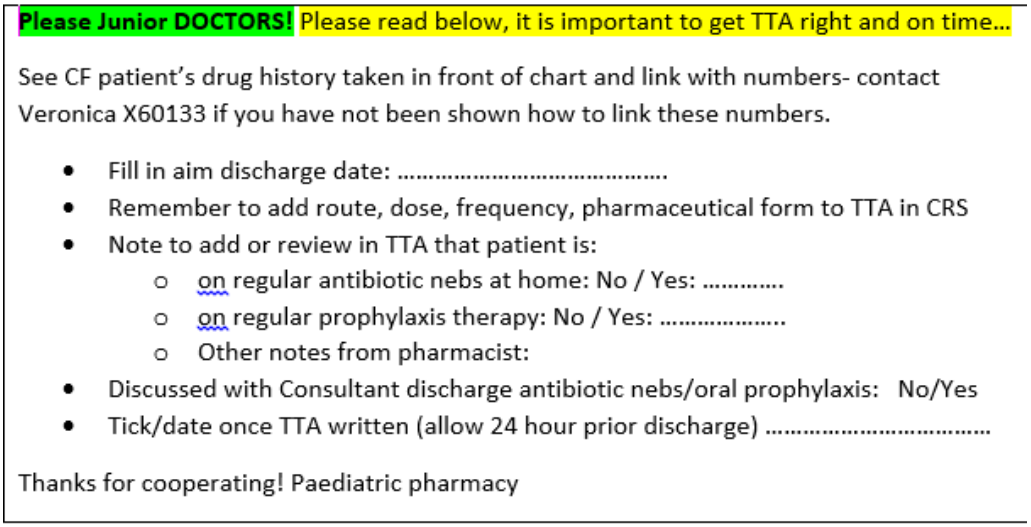
3.9.3. Prompt card.

The following agreed prompt card was attached to the drug chart after reconciling the medication on admission with the aim of prompting prescribers of common mistakes found in the retrospective phase (as well as with the new discharge computer system being used at discharge, CRS) and improve clarity of complex drug-therapies being stopped/restarted.

The card was added for each patient included in the prospective phase, which were all CF patients admitted to 7E Respiratory ward. The prompt card consisted of an A6 paper form containing the following information (Figure 3.10):

1. Estimated day of discharge.

2. Adding route of administration in CRS.
3. Adding dose in CRS.
4. Adding frequency in CRS.
5. Adding pharmaceutical form in CRS.
6. Prompting if the patient was regularly on nebulised antibiotics.
7. Prompting that patient usually takes prophylactic therapy with certain antibiotic.
8. Confirmation that junior doctor confirms with Consultant the restart of the regular nebulised and prophylactic antibiotics (points 6 and 7).



Please Junior DOCTORS! Please read below, it is important to get TTA right and on time…

See CF patient's drug history taken in front of chart and link with numbers- contact Veronica X60133 if you have not been shown how to link these numbers.

- Fill in aim discharge date: ……
- Remember to add route, dose, frequency, pharmaceutical form to TTA in CRS
- Note to add or review in TTA that patient is:
  - on regular antibiotic nebs at home: No / Yes: ……
  - on regular prophylaxis therapy: No / Yes: ……
  - Other notes from pharmacist:
- Discussed with Consultant discharge antibiotic nebs/oral prophylaxis: No/Yes
- Tick/date once TTA written (allow 24 hour prior discharge) ……

Thanks for cooperating! Paediatric pharmacy

Figure 3.10. Example of the prompt card designed and attached to patient's drug chart. *TTA: discharge electronic prescription, commonly named TTA for to take away medication from the hospital at discharge.

The prompt card was presented to the colleagues working in the respiratory ward and training was given to junior doctors and pharmacy colleagues covering respiratory ward.

3.9.4. Follow up of patients during hospital stay to identify the contributions to care made by pharmacist.

A closer follow up with monitoring of written pharmaceutical interventions suggested by the ward pharmacist during hospital stay. The written interventions were collected towards the end of the hospital stay by looking at the green pen interventions made on the drug chart by pharmacist and there were classified following the same classification as variable 26.

The verbal contributions were not captured as there was no capacity to organise this consistently due to the different pharmacists involved in the respiratory ward at the time of the prospective phase.

3.9.5. Drug listing pharmacy staff with conciliation at discharge.

The service of a drug listing pharmacy staff in some of the prescriptions was offered depending on the capacity of the pharmacy service. A member of the pharmacy paediatric team was either drug listing in CRS the regular medication of the children or reconciling the discharge prescription with the drug chart, prior to pharmacist validation. This way, the physical medication of the patient (newly started or medicines brought from home during that hospitalitzation) was checked in order to ensure that there would not be delays obtaining the medication required at discharge. The goal of this was to facilitate patient's discharge but indirectly this also helped to improve the quality of the prescriptions in CRS.

3.9.6. Communication with primary care.

Any communication needed with primary care prescribers was written in the prompt card (and the most relevant one was communicated to the CF consultant pharmacist) to make sure this was available to be captured at discharge. The discharge prescription was then checked for the type of communication provided, whether just conciliating errors picked up in primary care had been communicated or drug changes during hospital stay were documented or both.

3.10. Quality indicators.

The indicators were defined in order to evaluate the quality of the discharge prescription in the retrospective phase as well as evaluating the impact of the improvement actions taken to reduce medication error in discharge prescription during the prospective phase of the study.

Therefore, the quality indicators defined in this study were designed to make sure that:

- The most physiological organs affected in CF were receiving treatment, as per current practice in the Department.
- Correct prescribing of these drugs was optimised for age/weight.
- Pharmacotherapy was individualised per patient, in an effective and safely manner.

- Clarity of starting/stopping/restarting or review of the medication was provided.
- Communication with primary care doctors at discharge was achieved for patients to be able to get the right medicines in community.

3.10.1 Assessment of the quality of the prescription.

In this study the **quality of discharge prescription in children with CF** was evaluated taking into account the aspects indicated in the following common points 1 to 11 (for EPR, DL and CRS).

Table 3.6 summarises the definition and the way of calculating the quality indicators related to points 1 to 11, with the standard values, corresponding to the indicators of the **quality of discharge prescription in children with CF.**

Table 3.6. Definition of the quality indicators of the discharge prescription, how to calculate them, standard value for both parts of the study in which the indicators were applied.

Quality Indicator; Qi (description)	**Definition**	**Standard value (%)**	**Retros-pective**	**Pros-pective**
Qi 1 (identity)	Number of prescriptions with correct name and DOB* documented divided by the total number of prescriptions and multiplied by 100.	100	✓	✓
Qi 2 (weight)	Number of prescriptions with weight documented divided by the total number of prescriptions and multiplied by 100.	80	✓	✓
Qi 3 (allergy)	Number of prescriptions with allergies documented divided by the total number of prescriptions and multiplied by 100.	80	✓	✓
Qi 4 (vitamins in pancreatic insufficient children)	Number of prescriptions that contained lipophilic vitamins prescribed divided by the total number of prescriptions and multiplied by 100 (Pancreatic sufficient patients were not included in this quality indicator).	80	✓	✓
Qi 5 (Creon®)	Number of prescriptions that contained Creon® or another pancreatinin enzyme prescribed divided by the total number of prescriptions and multiplied by 100. (Pancreatic sufficient patients were not included in this quality indicator).	80	✓	✓
Qi 6 (drug)	Number of prescriptions identified with correct drugs and no interactions between two or more drugs (ig. fluconazole and itraconazol, two macrolides) divided by the number of prescriptions and multiplied by 100.	90	✓	✓

Qi 7 (dose)	Number of prescriptions with correct dose divided by the total number of prescriptions and multiplied by 100.	90	✓	✓
Qi 8 (frequency)	Number of prescriptions with correct frequency divided by the total number of prescriptions and multiplied by 100.	90	✓	✓
Qi 9 (pharmaceutical form)	Number of prescriptions with correct optimised pharmaceutical form divided by the total number of prescriptions and multiplied by 100.	90	✓	✓
Qi 10 (route)	Number of prescriptions with correct administration route divided by the total number of prescriptions and multiplied by 100.	90	✓	✓
Qi 11 (duration)	Number of prescriptions in which duration of certain medication like antibiotics or information regarding when to restart treatment was clear without any need of further clarification, divided by the total number of prescriptions and multiplied by 100.	90	✓	✓

*DOB: Date of birth.

3.10.2 Assessment of the quality of the prescription process

To evaluate **the quality of the prescription process** at **discharge** the specific points Qi 12-13 (for DL) were designed and were applicable exclusively in the retrospective phase, in which the quality of the discharge **prescription process** was evaluated taking into account the following points:

- The discharge letter was written (retrospective study).
- The date of the discharge letter: when the discharge letter was dated either the same day or two days from the date of discharge. In case that discharge letter was not written, variables related to drug therapy number 20 and 21 were considered as missing values (retrospective study).

The following Table 3.7 summarises the definition and the way of calculating the quality indicators related to quality to the prescription process (Qi 12 and Qi13).

Table 3.7. Definition of the quality indicators of the prescription process at discharge related to DL in the retrospective study, calculation and standard value used.

Quality Indicator: Qi (Description)	Definition	Standard value (%)	Retros-pective
Qi 12 (discharge letter)	Number of discharge letters written divided by the total of number of discharge patients and multiplied by 100.	80	✓
Qi 13 (date/delay of discharge letter)	Number of episodes which discharge letter were dated with 2 or less than 2 days of the discharge date divided by the total number of discharges, and multiplied by 100. (Excluding the patients whose discharge letter was not written).	80	✓

From the obtained values in the retrospective study it was possible to agree improvement strategies and these are described in the following section.

3.10.3 Assessment of the improvement actions implemented.

In order to improve global quality prescription at discharge the following **quality indicators for the improvement actions and safety strategies** were defined and implemented prospectively.

The following Table 3.8 summarises the definition and the calculation mode of the quality indicators used to evaluate the improvement actions defined from results obtained in the retrospective part of this study (Qi 14 to Qi18).

Table 3.8. Definition of the quality indicators of the discharge prescription related to the improvement actions implemented prospectively, calculation and standard values.

Quality Indicator: Qi (Description)	Definition	Standard value (%)	Prospective
Qi14 (medicines reconciliation, variable 24)	Number of admissions with medicines reconciliation on admission confirmed with a minimum of three or more sources of information divided by the total number of admissions and multiplied by 100.	80	✓
Qi 15 (prompt card, variable 25)	Number of drug charts that had a drug chart attached to it with information to address for discharge divided by the total number of admissions/discharges and multiplied by 100.	80	✓
Qi 16 (acceptation of interventions, variable 27)	Number of pharmaceutical interventions accepted after contributing to care divided by the total number of interventions made and multiplied by 100.	80	✓
Qi 17 (drug listing, variable 28)	Number of electronic prescriptions that had been either drug-listed or reviewed by pharmacy technician prior pharmacist validation divided by the total number of discharges and multiplied by 100.	60	✓
Qi 18 (communication with primary care, variable 30)	Number of electronic prescriptions that highlighted if changes or no changes had been made during hospital stay plus changes required in the repeat prescription divided by the total of number of discharge prescriptions and multiplied by 100.	80	✓

3.10.4 Assessment of the global quality

It was considered quality prescription in children with CF when the **global quality and safety indicator Qi 19** was greater than 50% (quality standard), which overlooked the following aspects, corresponding to the 6 rights:

1. The correct drug/s prescribed with not known drug interactions.
2. The correct dose for the age/weight of the patient.
3. The correct frequency for the patient.
4. The correct/most optimised pharmaceutical form for the patient.
5. The correct route of administration.
6. Duration and clear information on when to restart nebulised antibiotics or when to review new medication prescribed.

The global quality was assessed through the quality indicator showed in Table 3.9, in which all 6 rights had to be present for each drug prescribed in a full discharge prescription. This indicator was measured in both parts of this study (from the EPR in the retrospective, and from the CRS in the prospective).

Table 3.9. Definition of global quality indicator of the discharge prescription in CF children, calculation and standard value.

Quality Indicator: Qi (Description)	Definition	SV (%)	Retros-pective	Pros-pective
$Q_{i_{19}}^{EPR\ or\ CRS}$	Number of prescriptions that comply with each of the 6 rights defined Qi6-Qi11 divided by the total number of prescriptions and multiplied by 100.	50	✓	✓

SV: Standard value.

3.11. Data collection, data processing and statistical analysis.

The information collection during the retrospective study was carried by the same investigator directly by observing EPR and DL and entering this in excel for Windows®. A data collection form was created for the prospective study (see Figure 3.8) and this information was entered prospectively in the database prepared with excel program for Windows®. The statistic programme used was carried out with the formulas from excel spreadsheet[151,152,153]. Statistically significant differences were considered when the p value was < 0.05 and when p was <0.001 the differences were statistically highly significant.

3.11.1. Descriptive analysis.

Descriptive data presentation was performed depending on the type of data: quantitative or categorical data.

Quantitative data was described by statistic index based in momentous (mean, standard deviation and minimum/maximum) when they followed a normal distribution or by order based index (median and Harverage quartiles Q_1, Q_3) if they did not follow a normal distribution. Categorical data was shown as absolute frequencies and relatives (proportions or percentages) with 95% confidence interval.

The improvement opportunities were calculated per patient, per admission/discharge and per 100 drugs prescribed.

3.11.2. Analysis between variables.

Results were compared depending on the type of variables. Continuous variables and categorical variables were compared depending on the analysis needed for the type of variable and the way the results were distributed.

Mean comparison.

To test the assumption of normality, Kolmogorov-Smirnov test was applied and when normality of the variable was met, parametric tests were used. Student-t statistic test (when comparing two results) and Variance analysis (ANOVA) when more than two samples were compared.

In case of Student-t test for independent samples, the calculated statistics for each variable were mean, standard deviation and 95% confidence interval.

The statistics calculated values for each group were: mean, standard deviation and 95% confidence interval for the mean and ANOVA test of a factor was used to determine the effect of the quantitative variable.

Proportions/percentages comparison.

Chi squared (χ^2) was applied to compare proportions.

Due to the mixture of variables compared in the study, the observational study followed either a follow up study of cohorts (when there were two populations: one exposed and another one not exposed), in which the

Relative Risk (RR) was calculated; or a case-control type of study, in which the Odds Ratio (OR) was calculated. In both cases the information provided from the analysis was to understand the magnitude of the differences after applying Chi squared.

When the RR is greater than 1, informs that the proportion of the I.O is greater in the group of patients studied than in the control group of patients used as a reference. The exposed group was the validated by pharmacist and the not exposed group was the not validated by pharmacist (DL for instance).

The OR evaluates the probability to identify cases in the control group in relation to the other group. The control group was EPR and the other group was CRS in the prospective group. Statistical significance for OR was considered when the unit was not included in the 95% confidence interval.

3.11.3. Calculation of rates of improvement opportunities.

Improvement opportunities (I.O) were expressed per absolute number and per rate using the following formulas:

- *Rate of I.O per patient*: Division in which the numerator was the number of I.O and the denominator the number of total patients admitted.
- *Rate of I.O per admission/discharge:* Division in which the numerator was the number of I.O and the denominator the total number of admissions/discharges.

- *Rate of I.O per 100 drugs prescribed*: Division in which the numerator was the number of I.O and the denominator the total number of drugs prescribed. This quotient was multiplied by 100 (representing the 100 drugs prescribed).

3.11.4. Calculation of percentages of patients, discharges and drugs with improvement opportunities

- *Percentage of patients with I.O:* Division in which the numerator was the number of patients that had I.O and the denominator the total number of patients included in the variable studied, with the result multiplied by 100.
- *Percentage of episodes (discharges or admissions when improvement strategies and safety actions were implemented) with I.O*: Division in which the numerator was the number of episodes (discharges or admissions) that had I.O and the denominator the total number of discharges/admissions included in the variable studied, with the result multiplied by 100.
- *Percentage of drugs with I.O:* Division in which the numerator was the number of drugs that had I.O and the denominator the total number of drugs included in the variable studied, with the result multiplied by 100.

3.11.5. Calculation of quality indicators.

The definition and calculation of each quality indicators and the global quality indicator is explained in their corresponded Tables 3.6-3.9 in section 3.10.1.

4. Results

4.1. Retrospective phase.

4.1.1 Patients.

A total of 108 paediatric CF patients were registered in the CF system during the years of 2013 and 2014, being 56 (52%) males and 52 (48%) females.

During the retrospective phase of 24 months, the number of discharges (episodes) that followed the inclusion criteria was 100 which corresponded to 42 CF children, representing 39% of the total children with CF registered in the data base of the RLH (n=108). Of these 42 children, 16 (38%) were boys and 26 (62%) were girls, with a mean age of 9.8 years $\pm$ 4.43 (min 1, max 17). The mean of admissions per patient was 2.43 $\pm$ 2.04, with a minimum of 1 and a maximum of 8 admissions.

There was no opposition from any of the parents to being part of the study.

4.1.2. Variables.

The studied variables are presented in two different sections describing patient and hospital stay variables in the first section; and drug therapy variables in the second section. Each section has the information that relates to electronic prescription (EPR) and discharge letter (DL).

4.1.2.1. Related to patient and hospital stay variables.

The following Table 4.1 represents the characteristics of the children studied together with hospital stay variables.

Table 4.1. Demographic variables of the number of episodes of the patients included in the retrospective phase (n=100).

#	Variable	Results
1	Age (mean ± SD, min-max)	10.5 ± 3.9 (1-17)
2	Gender n; % (95%CI) male	31; 31 (22.78-40.63)
	female	69; 69 (59.37-77.22)
4	Associated pathologies n; % (95%CI)	
	• Pancreatic insufficient	98; 98 (93-99.45)
	• GORD	73; 73 (63.57-80.73)
	• CF related diabetes	31; 31 (22.78-40.63)
	• Liver disease/Gallstones	17; 17 (10.89-25.55)
	• Other	53; 53 (43.29-62.49)
3	Number associated pathologies per patient n; % (95%CI)	
	• 1	13; 13 (7.76-20.98)
	• 2	31; 31 (22.78-40.63)
	• 3	29; 29 (21.01-38.54)
	• 4	27; 27 (19.27-36.43)
	• 5	0; 0 (0-3.7)
6	Reason for admission n; % (95%CI)	
	• Infective exacerbation	45; 45 (35.61-54.76)
	• Elective	55; 55 (45.24-64.39)
7	Hospital stay (mean ± SD, min-max)	12.8 ± 4.2 (2,22)
10	Days of discharge n; % (95%CI)	
	• Monday-Friday	81; 81 (72.22-87.49)
	• Saturday-Sunday	19; 19 (12.51-27.78)

#: Number of variable; n: number; SD: standard deviation; 95%CI: 95% confidence interval; GORD: gastro oesophageal reflux disease.

4.1.2.2. Related to drug therapy variables.

Table 4.2 summarises the information related to drug therapy variables: weight, allergies and type of prescriber/validating pharmacist.

The DL complements the electronic prescription at discharge (EPR) and have a section of medicines. A total of 76% of the discharges had a DL that complemented EPR.

From the total of 100 discharges, the children's **weight** was documented in 85 (85%; 95%CI: 76.72-90.69) EPR and in 75 (98.68%; 95%CI: 93-99.45) DL. There were two electronic prescriptions without the weight being documented and without a discharge letter, this corresponds to a 13% of discharges with no information on the patient's weight at all on that episode.

Allergies were recorded in 98% of the electronic prescriptions, however only 34 (44.74%; 95%CI: 34.08-55.90) of the DL had allergy information documented indicating either the allergies the patient had or that there were no known allergies. There was no letter found corresponding to any allergic child whose allergies had not been documented, the key information in allergic children was present in DL.

Table 4.2. Weight, allergies documented, type of prescriber and pharmacist documented in the electronic prescription (EPR) or discharge letter (DL) of patients included in the retrospective phase.

#	Drug-therapy variables	EPR n=100	DL n=76	P
11	Weight documented %; (95%CI)	85.00; (76.72-90.69)	98.68; (92.92-99.77)	0.002
12	Allergies documented %; (95%CI)	98.00; (93.00-99.45)	44.74; (34.08-55.90)	<0.001
15	Prescribing doctor			
	Junior %; (95%CI)	100.00; (96.30-100)	90.79; (82.19-95.47)	0.002
	Senior/clinical fellow (%)	0.00; (0-3.7)	9.21; (4.53-17.81)	0.002
16	Pharmacist validation (Y/N %)	85/15		
	Junior %; (95%CI)	73.00; (63.57-80.73)	N/A	
	Senior %; (95%CI)	12.00; (7.00-19.81)		

#: Number of variable; n: number; N/A: not applicable; Y: yes; N: no; p: statistical value.

On all occasions the **prescriber** of EPR was a Junior Doctor. Most DL were signed by ST2-ST3 and only 7 (9.21%; 95%CI: 4.53-17.81) by a Clinical Fellow/Registrar. All DL had the name of the Consultant next to the electronic signature of the junior/registrar signing the prescription.

During the retrospective study, a **clinical pharmacist** had validated 85 (85%; 95%CI: 76.72-90.69) electronic prescriptions at discharge and 73 of them (73%; 95%CI: 63.57-80.73) corresponded to validation by junior pharmacist. No DL were checked by any pharmacist.

Table 4.3 summarises the number and types of **drugs** prescribed in EPR and in the medication section in the DL, as well as the number and percentage of drugs prescribed in EPR as brand name.

Table 4.3. Drug-therapy variables.

#	Variables related to drug –therapy	EPR n=100	DL n=76
21	Number of drugs	1343	984
	Mean number of drugs ± SD (min,max)	13.4 ± 3.9 (6,27)	12.9 ± 3.3 (7,24)
14	Type of drugs prescribed (%)		
	Nebulised mucolytics	100	100
	Anti-reflux drugs	95	100
	Pancreatinin	98	100
	Lipophilic vitamins	97	100
	Nebulised antibiotics	76	85
	Salbutamol inhaled	97	89
	Oral or IV antibiotics	75	70
22	Drugs as brand name n; % (95%CI)	375; 27.92 (25.59-30.38)	-

#: Number of variable; EPR: electronic prescription used at discharge in the retrospective phase; DL: discharge letter; n: number; SD: standard deviation.

No statistical diferences were found between the mean number of drugs prescribed in EPR and DL (p= 0.370).

From the 1343 total drugs prescribed electronically, 375 (27.92%; 95%CI: 25.59-30.38) were prescribed as **brand names** (with a mean of 3.8 ± 1.73 brand names per patient, min 1 and max 9). The most common brand names prescribed were Creon®, AquADEKs®, Colistin® and Promixin®.

Table 4.4 summarises the **administrative analysis** conducted on the DL from patients included in the retrospective phase.

Table 4.4. Analysis of the discharge letter of patients included in the retrospective phase and comparison with EPR of the same patients.

#	Variables of the discharge letter	
18	Discharges with DL n; % (95%CI)	76; 76.00 (66.77-83.31)
19	Delay of DL (days) mean ± SD (min,max)	5,6 days ± 7.6 (min 0, max 37)
	0-2days of delay n; % (95%CI)	35; 46.05 (35.31-57.18)
	≥ 3 days delayed n; % (95%CI)	41; 53.95 (42.82-64.69)
20	Number of DL with discrepancies when compared with EPR n; % (95%CI)	75; 98.68 (92.92-99.77)

#: Number of variable; n: number; 95%CI: 95% confidence interval.

4.1.3. Improvement opportunities.

Improvement opportunities (I.O) were evaluated in EPR and DL. The DL was analysed in comparison with EPR and **discrepancies** were noted. A total of 533 I.O were identified, 165 (30.96%; 95%CI: 27.18-35.01) in EPR and 368 (69.04%; 95%CI: 64.99-72.82) in DL. The results obtained are shown in the next points, according to both sources of information evaluated (EPR and DL).

- EPR:
    - From 100 discharges (EPR) 81 (95%CI: 72.22-87.49) of them had **improvement opportunities** (I.O). These 81 EPR with I.O corresponded to 33 (78.57%; 95%CI 64.06-88.29) patients of the total of 42 patients included in this phase of the study.
    - In these 81 EPR with I.O a total of 165 I.O were detected, 17 of them (10.30%; 95%CI 6.53-15.88) related to non-medication errors I.O, whilst 148 (89.70%; 95%CI 84.12-93.47) corresponded to **medication errors.** In these 81 EPR, there were 1123 (83.62%; 95%CI 81.54-85.50) drugs prescribed of the total of 1343.
    - The percentage of drugs with I.O was 12.28% (95%CI 10.64-14.15).
- DL:
    - From the 100 discharges, there were 76 discharge letters and 75 (98.68%; 95%CI 92.92-99.77) of them had **non-justified discrepancies** (or improvement opportunities) when comparing with EPR (conciliation errors). These 76 DL corresponded to 39 (92.86%; 95%CI: 80.99-97.54) patients and the 75 DL with I.O also corresponded to 39 patients.
    - There were 368 **improvement opportunities**, in which 35 (9.51%; 95%CI: 6.92-12.94) of them corresponded to non-medication errors and the rest 333 (90.49%; 95%CI: 87.06-93.08) were **medication errors**. The total number of drugs prescribed in DL with I.O was 968 which corresponded to a

98.37% (95%CI: 97.38-99.00) of the total drugs in the DL (984 drugs prescribed in the total DL).

- The percentage of drugs with I.O was 37.40 % (95% CI: 34.43-40.47).

The above information is summarised in Figure 4.1.

The percentage of patients with I.O, discharges with I.O and drugs with I.O found in EPR and DL is revealed in Table 4.5.

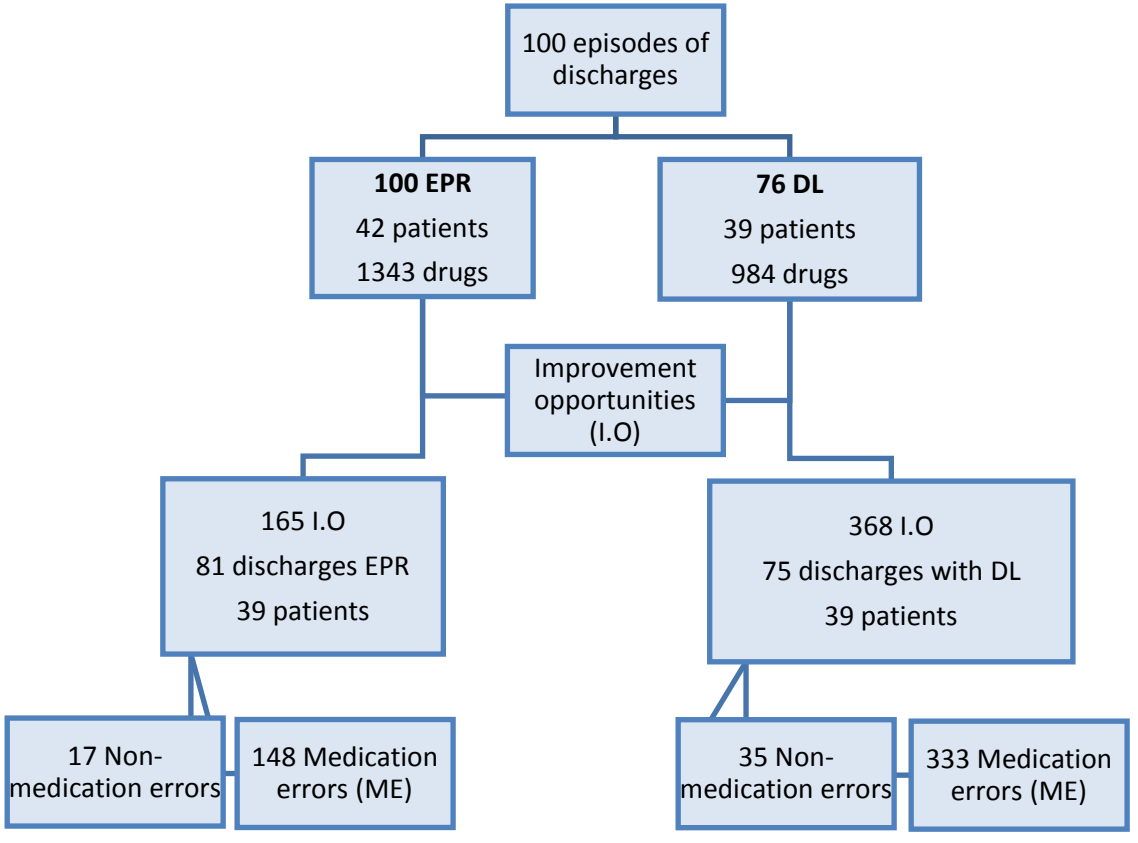


Figure 4.1. Diagram and characteristics of the 100 episodes included in the retrospective phase.

Table 4.5. Percentages of patients and discharges with improvement opportunities found in EPR and DL.

#	EPR n=100		DL n=76		p value
	Number, percentage (95%CI) of # with I.O				
Patients	39	92.86 (80.99-97.54)	39	100 (91.03-100)	0.091
Discharge	81	81.00 (72.22-87.49)	75	98.68 (92.92-99.77)	<0.001

N: Number; EPR: Electronic prescription report; DL: Discharge letter; I.O: improvement opportunities; 95%CI: 95% confidence interval.

Statistically significant differences between I.O in the DL and EPR were obtained when analising the number of discharges and the total of number of drugs prescribed.

The relative risk of the percentage of discharges with I.O (EPR and DL) has a value of 1.21(95%CI: 1.10-1.34), informing that the proportion of having DL with I.O is 1.21 times greater than in EPR.

The following Table 4.6 shows the I.O studied in EPR and DL expressed as rates per patient, per discharge (episode) and per 100 drugs prescribed.

Table 4.6. Improvement opportunities expressed per patient, per discharge, and per 100 drugs prescribed.

IMPROVEMENT OPPORTUNITIES								
	EPR				DL			
		Total	**Non-ME**	**ME**		**Total**	**Non-ME**	**ME**
	n (%)	165	17 (10.30)	148 (89.70)		368	35 (9.5)	333 (90.5)
	RATE OF IMPROVEMENT OPPORTUNITITES PER #							
#	**n**				**n**			
Patient	42	3.93	0.39	3.54	39	9.46	0.9	8.56
Discharge	100	1.65	0.17	1.49	76	4.84	0.46	4.38
100 drugs prescribed	1343	12.28*	1.23	11.06	984	37.4*	3.6	33.85

n: Number; EPR: Electronic prescription report; DL: Discharge letter; * Statistical Test $_{x}^{2}$ p<0.001.

4.1.3.1. Improvement opportunities classified by pharmacist validation.

The I.O in EPR prescriptions at discharge previously **validated or not validated by pharmacist** are summarised in Table 4.7.

Table 4.7. Number of I.O that were observed in EPR during the retrospective phase according to validation by pharmacist.

		IMPROVEMENT OPPORTUNITITES in EPR		
	n	**Total (n)**	**Non-ME n (%)**	**ME n (%)**
Total	100	165	17 (10)	148 (90)
Validated by pharmacist	85	117	1 (0.85)	116 (99.15)
Not validated by pharmacist	15	48	16 (33.3)	32 (66.7)

n: number; ME: medication error.

- There were 85 (85%; 95%CI: 76.72-90.69) EPR validated by a pharmacist corresponding to 37 patients with a total of 1161 drugs. From the 85 EPR validated by a pharmacist, 69 (81.18%; 95%CI: 71.59-88.07) of them had I.O corresponding to 30 patients with a total of drugs prescribed of 975 and a total of 117 (10.08%; 95%CI: 8.48-11.94) drugs with I.O.
- There were 15 (15%; 95%CI: 9.31-23.28) EPR not validated by a pharmacist which corresponded to 12 patients with a total of 182 drugs. From these 15 EPR not validated by a pharmacist, 12 of them had I.O (80%; 95%CI: 54.81-92.95) corresponding to 10 patients with a total of 148 drugs prescribed in which there were 48 (26.37%; 95%CI: 20.51-33.22) I.O.

The following Table 4.8 shows the percentage of discharges with I.O and percentage of drugs with I.O found in EPR when prescriptions were

validated and were not validated by pharmacist. The results of the number of patients with I.O were not expressed due to limitations of the study, as they were a possible confounding factor.

Table 4.8. Percentages of discharges and drugs prescribed with improvement opportunities found when EPR was validated and not validated by the pharmacist.

#	Validated by pharmacist n discharges=85 n drugs=1161	Not validated by pharmacist n discharges=15 n drugs=182	Relative risk (95%CI)
	Percentage (95%CI) of # with I.O		
Discharge	81.18 (71.59-88.07)	80.00 (54.81-92.95)	0.99 (0.75-1.29)
Total drugs prescribed	10.08* (8.48-11.94)	26.37* (20.51-33.22)	2.62 (1.94-3.52)

n: number; I.O: improvement opportunities; EPR: electronic prescription used at discharge during the retrospective study; *: χ^2, p<0.001.

The percentage of validated and not validated by pharmacist discharges with I.O did not show a statistically significant difference. However, the percentage of I.O per total drugs prescribed showed statistically significant differences and the proportion of identified drugs with I.O was 2.62 times greater in non validated prescriptions.

Table 4.9 presents the number of I.O per episode of discharge EPR according to validation by pharmacist and to the type of I.O.

And Table 4.10 represents the days of the week in which EPR were mainly prescribed when the patient was discharged.

Table 4.9. I.O detected in EPR discharge prescriptions in the retrospective phase when the discharge prescription was validated and was not validated by pharmacist.

	Validated by pharmacist				**Non-validated by pharmacist**			
	n	Total	Non ME	ME	n	Total	Non ME	ME
	85	117	1 (0.86)	116 (99.14)	15	48	16 (33.3)	32 (66.7)
#	**Number and rate of # with I.O classified according to non-ME and ME**							
Discharge	85	1.38	0.01	1.37	15	3.2	1.07	2.13
100 drugs prescribed	1161	10.08	0.09	9.99	182	26.37	8.78	17.59

n: number; I.O: improvement opportunities; EPR: electronic prescription used at discharge during the retrospective study; ME: medication error.

Table 4. 10. Distribution of discharges and medication errors classified by day of the week of the discharge and the p value of the parameters analysed.

	Monday-Friday (n=81)	**Saturday-Sunday (n=19)**	**p**
Discharge with I.O n (%)	68 (83.95)	13 (68.42)	0.122
ME (n)	124	24	
ME per discharge	1.53	1.26	0.210
Drugs prescribed (n)	1096	247	
ME per 100 drugs prescribed	11.31	9.72	0.471

n: number; ME: Medication error; I.O: Improvement opportunitities; p: statistical value.

Furthermore, Table 4.11 summarises the I.O of medication errors in EPR classified according to discharge prescription validation or not by pharmacist and by day of discharge: Monday-Friday/Saturday-Sunday.

Table 4. 11. Distribution of discharges and medication errors classified taking into account pharmacist validation and day of the week.

	Validated discharges (n=85)		**Non-Validated discharges (n=15)**	
	Monday-Friday (n=72)	**Saturday-Sunday (n=13)**	**Monday-Friday (n=9)**	**Saturday-Sunday (n=6)**
Discharge with I.O n (%)	60 (83.3)	9 (69.23)	8 (88.89)	4 (66.67)
ME (n)	101	15	23	9
ME per discharge	1.40	1.15	2.56	1.5
Drugs prescribed (n)	997	164	99	83
ME per 100 drugs prescribed	10.13	9.15	23.23	10.84

n: number; ME: Medication error; I.O: Improvement opportunitities.

Non statistically significant differences were reveled between discharges containing I.O validated and not validated during week days (83.3 % vs 88.89%) and weekend (69.23% vs 66.67%).

Differences between the proportion of ME detected at discharge during the week when the prescriptions had not been validated, (1.40 vs 2.56 p=0.790) or during the weekend (1.15 vs 1.5) when the prescriptions had been or had not been validated (p=0.951) were not statistically significant.

Medical errors expressed per 100 drugs prescribed when prescriptions were or were not validated during the week showed significant differences (10.13 vs 23.23, p<0.001). However, when prescriptions were or were not validated during the weekend there were no statistically significant differences (9.15 vs 10.84, p=0.673).

4.1.4. Medication errors

The following epigraphs correspond to classification and causes of the medication errors (ME).

4.1.4.1. Classification of the ME.

- The total number of ME found in EPR was 148 (116 from discharges validated and the rest of them from discharges not validated by the pharmacist) with a mean of 1.48 ME $\pm$ 1.38 (min 1, max 7). This corresponded to 11% ME of the total medication prescribed.
- The total number of ME found in DL were 333, in 75 (98.6%) of the total DL analysed (76). The mean number of ME per discharge letter

was 4.44 ± 2.23 (min 1, max 10). This corresponds to a 33.8% of ME of the total medication listed in the discharge letters.

The number, mean with standard deviation (SD) of ME and the percentage of types of ME detected in EPR and DL is summarised in Table 4.12.

Table 4.12. Mean and standard deviation (SD) values of medication error per EPR or DL, and number and percentage (%) of medication errors detected in EPR and in DL classified according the type of medication error indicated in section 3.6.

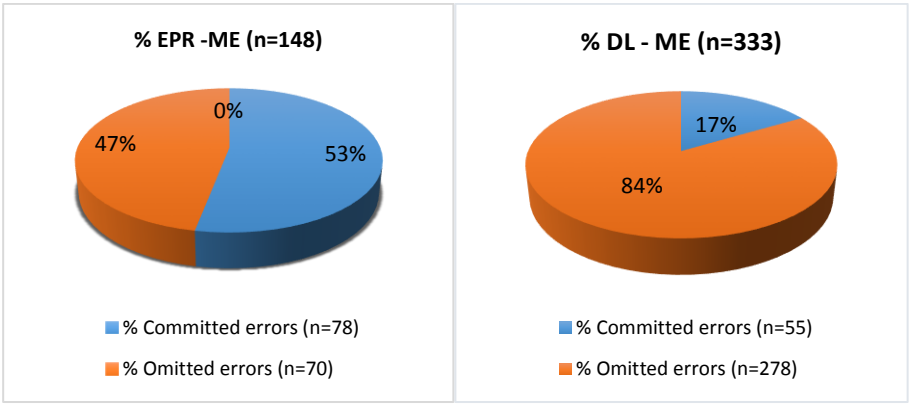
	Medication error		**Statistics tests**	
	EPR	DL	P	RR (95%CI)
Number of ME	148	333		
Mean ± SD (min, max)	1.48 ± 1.38 (1,7)	4.44 ± 2.23 (1,10)	<0.001	
n of ME per 100 drugs prescribed at discharge	11.02	33.84	<0.001	
Type of ME	**n; (%) (95%CI)**	**n; (%) (95%CI)**		
Drug	38; 25.68 (19.32-33.27)	23; 6.91 (4.65-10.15)	<0.001	0.27 (0.17-0.43)
Dose	35; 23.65 (17.52-31.11)	79; 23.72 (19.47-28.58)	0.987	1.00 (0.71-1.42)
Frequency	3; 2.03 (0.69-5.79)	35; 10.51 (7.65-14.27)	0.002	5.19 (1.62-16.59)
Duration	25; 16.89 (11.71-23.75)	16; 4.80 (2.98-7.66)	<0.001	0.28 (0.16-0.52)
Pharmaceutical form	44 ; 29.73 (22.95-37.53)	111 ; 33.33 (28.49-38.56)	0.436	1.12 (-0.50-0.16)
Route of administration	3 ; 2.03 (0.69-5.79)	69 ; 20.72 (16.71-25.40)	<0.001	10.22 (3.27—31.95)

n: Number; SD: standard deviation; ME: Medication error; p: statistical value; RR: Relative risk; 95%CI: 95 Confidence interval.

ME of route of administration and frequency were higher in DL than in EPR, with statistically significant differences; whilst ME of drug and duration (mainly omitted or continued drugs from the hospital stay) were higher in EPR than in DL, with significant differences.

- With regard to the subtype of medication errors:
    - In EPR, from the 148 medication errors, the number of committed errors found were 78 (52.70%; 95%CI: 44.96-60.58%) and these were detected in 49 (49%) EPR. The errors due to omitted information were 70 (47.30; 95%CI: 39.42-55.31), and these were also found in 49 (49%) EPR.
    - In DL, from the 333 errors, 55 (16.52%; 95%CI: 12.91-20.88) of them were committed errors, which were found in 43 (57%) DL. On the other hand, 278 (83.48%; 95%CI: 79.12-87.09) were omission errors and were found in 72 (94.74%; 95%CI: 87.23-97.93) DL.

Figure 4.2 represents the percentage of the subtype of medication errors in EPR and DL.



ME: Medication error; n: number.
Figure 4.2. Percentage of omitted and committed errors in EPR and DL.

The **type (6 rights) and subtype (committed or omitted) of medication errors** are detailed below per each source of information used.

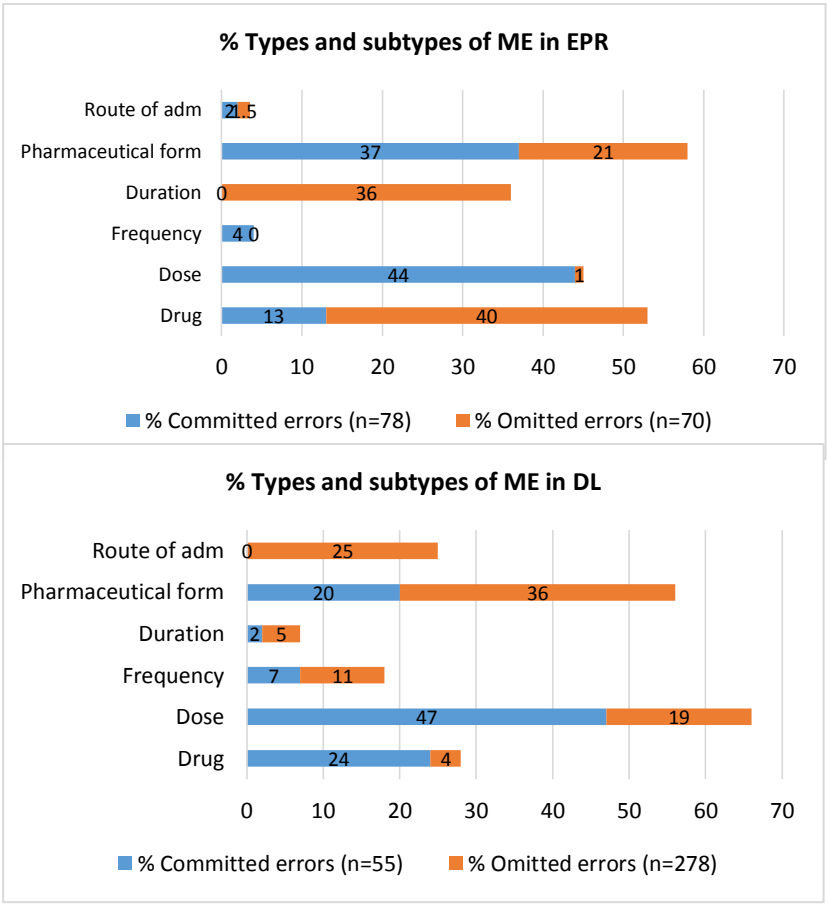
The following Table 4.13 summarises the types and subtypes of ME found in EPR and DL, followed by Figure 4.3 which represents the percentage of ME in EPR and DL classified by the types and subtypes defined in section 3.7.1.

Table 4.13. Percentage of medication errors committed and omitted observed in electronic prescription recorded (EPR) and Discharge letter (DL).

Type and subtype of ME	**Percentage of medication errors**			
	Committed		**Omitted**	
	EPR n (%) (95%CI)	**DL n (%) (95%CI)**	**EPR n (%) (95%CI)**	**DL n (%) (95%CI)**
Drug	10 (12.82) (7.12-22.02)	13 (23.64) (14.37-36.35)	28 (40) (29.33-51.71)	10 (3.60) (1.97-6.49)
Dose	34 (43.59) (33.14-59.64)	26 (47.27) (34.69-60.21)	1 (1.43) (0.25-7.66)	53 (19.06) (14.88-24.09)
Frequency	3 (3.85) (1.32-10.71)	4 (7.27) (2.86-17.26)	0	31 (11.15) (7.97-15.39)
Duration	0	1 (1.82) (0.32-9.61)	25 (35.71) (25.50-47.41)	15 (5.40) (3.30-8.71)
Pharm form	29 (37.18) (27.29-48.27)	11 (20) (11.55-32.36)	15 (21.43) (13.44-32.39)	100 (35.97) (30.56-41.77)
Route of adm	2 (2.56) (0.71-8.88)	0	1 (1.43) (0.25-7.66)	69 (24.82) (20.11-30.22)

The main committed errors in EPR corresponded to dose and pharmaceutical form. In DL the committed errors were also dose and drug followed by pharmaceutical form. Omitted errors were greater in DL than in EPR. In the DL the main information omitted was in pharmaceutical form and route of administration, whilst in EPR the main omissions found were in drug and duration.

The next Figure 4.3 represents the total ME observed in EPR and in DL according to the types and subtypes defined in section 3.7.1.



ME: Medication errors; n: number.
Figure 4.3. Percentage of subtypes of ME in EPR and EDL.

4.1.4.2. Medication errors: causes.

The most probable **causes** of the medication errors observed in EPR and DL are summarised in Table 4.14.

Table 4.14. Cause of Medication Errors in EPR and DL in the retrospective phase (in EPR and DL) with justification and estimated percentage evaluated.

Cause	Justification of the causes	%
Organizational	Rotation time for CF speciality. Different prescriptions used and difficulties to check each one to confirm reconciliation. Lack of prioritisation and DL/EPR written up late, therefore screened late. Pharmacist validated out of hours despite weekday. Overload of tasks to fulfill.	40
Educational	Junior staff in front of complex cases in short period of time. Figure of educational pharmacist for CF not totally set up during 2013. Junior pharmacist covering respiratory ward.	30
Technological	Different systems of prescriptions. Lack of alert systems.	15
Human	Forget, lapse in concentration.	5
Communication	Not applicable as not identified retrospectively	-

CF: Cystic Fibrosis

4.1.5. Quality indicators.

The following epigraphs summarise the results of the quality indicators described in patients and methods section 3.10.

4.1.5.1. Quality of the prescription.

Table 4.15 represents the difference of the quality indicators in EPR and DL, with the statistical tests conducted to evaluate the results.

Table 4.15. Quality indicators of the medication at discharge in EPR and DL. Standard value, χ^2 p value and Relative risk with 95% confidence interval (CI).

Quality Indicator (Qi)	**Standard value**	**EPR (n=100)**	**DL (n= 76)**	**P**	**RR (95%CI)**
Qi 1 (identity)	100	100.00	100.00	N/A	N/A
Qi 2 (weight)	80	85.00	98.68	0.002	1.16 (1.07-1.27)
Qi 3 (allergy)	80	98.00	44.74	<0.001	0.46 (0.36-0.59)
Qi 4 (vitamins)	80	97.00	100.00	0.129	N/A
Qi 5 (Creon®)	80	100.00	100.00	N/A	N/A
Qi 6 (drug)	90	70.00	69.73	0.969	0.99 (0.82-1.21)
Qi 7 (dose)	90	73.00	39.47	<0.001	0.54 (0.39-0.73)
Qi 8 (frequency)	90	97.00	63.16	<0.001	0.65 (0.55-0.78)
Qi 9 (pharm form)	90	66.00	15.79	<0.001	0.24 (0.14-0.41)
Q 10 (route)	90	97.00	46.05	<0.001	0.48 (0.37-0.61)
Qi 11 (duration)	90	82.00	82.89	1.000	1.01 (0.88-1.16)

n: number; N/A: not applicable to the retrospective study.

Recorded weight and duration of the treatment was recorded in DL in greater proportion than in EPR. The other variables were prescribed correctly in greater proportion in EPR.

4.1.5.2. Quality of the prescribing process at discharge.

Table 4.16 shows the administrative quality indicators of the discharge process in DL.

Table 4.16. Quality indicators of the discharge process (administrative analysis of the DL).

Quality Indicator (Qi)	Standard value	DL n= 76
Qi 12 (discharge letter)	80	76
Qi 13 (date/delay of discharge letter)	80	46

n: number; DL: discharge letter.

4.1.5.3. Global quality and safety of the children CF prescription.

Table 4.17 represents the global quality of paediatric CF prescriptions when considered EPR and DL separately. The last column shows the global quality combining EPR and DL for the same episode.

Table 4.17. Total quality indicators values for EPR and DL and Global combined EPR and DL quality indicator and excellence value during the retrospective phase.

Quality Indicator (Qi)	Standard value	EPR n=100	DL n= 76	n EPR and DL with same correct 6R
Qi 19	50	22.00	9.21	5

n: number; EPR: electronic prescription at discharge used in the retrospective study; DL: discharge letter; 6R: 6 rights (defined section 3.7.1)

The global combined quality indicator of discharge, combining EPR and DL gave a value of 5, indicating the information related to medication at discharge in the DL reduces the global quality of the process of discharge.

Taking into account EPR exclusively, the quality of the process does not achieve the standard defined: 2 of the 6 Rights variables comply with the 90% value stated (frequency and route) although other variables of the

process like identity, weight, allergy and medicines to be prescribed in paediatrics like vitamins and Creon® achieved much higher values than the 90% of the standard value.

4.1.6. Justification of the safety actions and improvement strategies for the prospective phase.

According to the results obtained in the retrospective phase and with the agreement with the main prescribers for the prospective phase, Figure 4.4 represents the safety actions associated with these causes, as well as the improvement strategies implemented in the prospective phase (also explained in section 3.10).

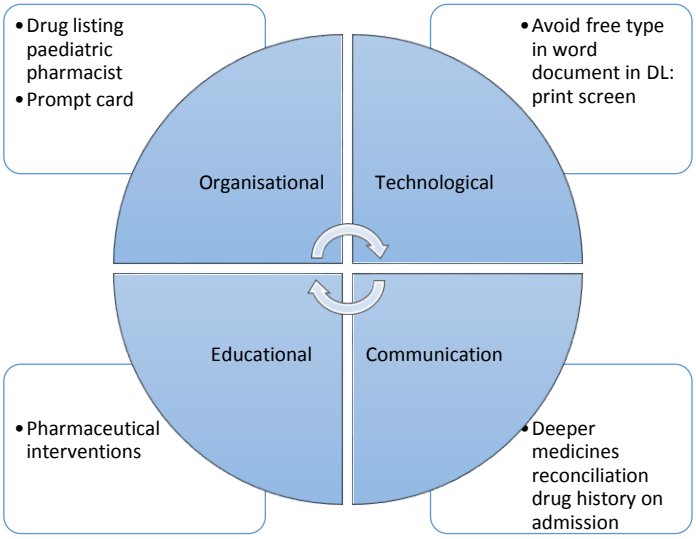


Figure 4.4. Safety actions and improvement strategies to be applied in the prospective phase.

4.2. Prospective phase.

4.2.1. Patients.

During the 8 month prospective phase of the study (May-December 2016), there were over 65 admissions of children with CF to the RLH, 58 to the respiratory ward 7E, and 56 (97%) of them followed inclusion criteria. There was one case not included in the study due to failure of attaching the prompt card to the drug chart and medicines reconciled with two sources of information, so 55 (98%) admissions were included. These admissions corresponded to 35 different patients, 14 (40%) of them boys and 21 (60%) girls, with a mean age of 10.11 years $\pm$ 3.89 (min 3, max 16). The mean admissions per patient were 1.6 $\pm$ 0.8 (min 1, max 4).

There was no opposition from any of the parents to check primary care repeat prescription records.

4.2.2. Variables.

The studied variables are presented in two different sections: those related to the patient and hospital stay in the first section and those related to the drug therapy in the second. Each section has the information that relates to reconciliation, primary care, interventions during hospital stay and discharge.

4.2.2.1 Related to patient and hospital stay.

Table 4.18 describes the patient demographics and hospital stay variables defined for this study.

Table 4.18 Demographic variables of the number of episodes of the patients included prospectively.

#	Variable	Results (n=55)
1	Age, mean ± SD, (min, max)	10.2 ± 3.9 (2,16)
2	Gender n; % (95%CI) male female	19; 34.55 (23.36-47.75) 36; 65.45 (52.25-76.64)
4	Associated pathologies n; % (95%CI) 1. Pancreatic insufficient 2. GORD 3. CF related diabetes 4. Liver disease/Gallstones 5. Other	 51; 92.73 (82.74-97.14) 37; 67.27 (54.10-78.19) 16; 29.09 (18.77-42.14) 18; 32.73 (21.81-45.90) 22; 40.00 (28.12-53.19)
3	Number associated pathologies per patient n; % (95%CI) • 1 • 2 • 3 • 4 • 5	 7; 12.73 (6.30-24.02) 15; 27.27 (17.28-40.23) 21; 38.18 (26.52-51.39) 12; 21.82 (12.95-34.37) 0; 0 (0-6.53)
5	Language of parents n; % (95%CI) • English as first language • English not first language	 38; 69.09 (55.97-79.72) 17; 30.91 (20.28-44.03)
6	Children living with parents in same house n; % (95%CI) • With one parent • With two parents	17; 30.91 (20.28-44.03) 38; 69.09 (55.97-79.72)
7	Reason for admission n; % (95%CI) • Infective exacerbation • Elective	 35; 63.64 (50.42-75.07) 20; 36.36 (24.93-49.58)
8	Hospital stay in days, mean ± SD, (min, max)	13.8 ± 2.4 (6, 21)
9	Days of admission n; % (95%CI) • Monday-Friday • Saturday-Sunday	 46; 83.64 (71.74-91.14) 9; 16.36 (8.86-28.26)
10	Days of discharge n; % (95%CI) • Monday-Friday • Saturday-Sunday	 49; 89.09 (78-94.90) 6; 10.91 (5.10-21.83)

#: number of variable; SD: standard deviation; n: number; 95%CI: 95% confidence interval.

4.2.2.2 Related to drug therapy.

Table 4.19 summarises the information related to drug therapy variables: weight, allergies and type of prescriber/validating pharmacist.

All drug charts had **weight** documented (100%) during admission. No weight was documented in the primary care repeat prescriptions section. Weight was documented in all discharge prescriptions, however when the computer system transcribed the information in the final document, weight was only present in 36 final reports, 65.5% of the total of 55 analysed.

There were two drug charts during drug history reconciliation on admission (3.6%) with the **allergy** section left blank but this was rectified during reconciliation. From 55 primary care prescriptions checked, 40 of them (72.73%; 95%CI: 59.77-82.72) had matched allergies of the children with the real most updated allergies, and in 15 (27.27%; 95%CI: 17.28-40.23) cases the allergies documented were not accurate. These 15 primary care prescription corresponded to 10 patients. In 50 (91%) discharges, CRS had allergies recorded in the final electronic prescription (although they were documented in all CRS prescriptions but not transcribed in the final report).

Table 4.19. Weight, allergies documented, type of prescriber and pharmacist recorded for patients included in the prospective study.

#	Variable	Drug therapy variables measured in:		
		Reconciliation in		Discharge
		Admission	PC prescription	CRS
11	Weight n (%)	55 (100)	Not found	36 (65.45)
12	Allergies (%)	53 (96.36)	40 (72.73)	50 (90.91)
15	Prescribing n (%) • Junior doctor • Pharmacy staff	55 (100%)	N/A	 40 (72.73) 15 (27.27)
28	Pharmacy technician review after prescribing and previous validation n (%)	N/A	N/A	34 (61.82)
16	Pharmacist validation (Yes) n (%) • Junior • Senior	N/A	N/A	50 (90.91) 15 (30) 35 (70)

#: Number of variable; PC: primary care; CRS: Clinical Records System; n: number; N/A: not applicable.

On 40 (72.73%; 95%CI: 59.77-82.72) occasions the **prescriber** of the *discharge* prescriptions were junior doctors, and 15 (27.27%; 95%CI: 17.28-40.23) were a pharmacy member. The name of the doctor writing the report was not present in the final report, it was the name of the consultant at discharge showing in the report.

A total of 50 (90.91%; 95%CI: 80.42-96.05) *discharge* prescriptions were **validated by pharmacy:** 70% (95%CI: 56.25-80.90) by a senior paediatric pharmacist and the remainder by junior rotational pharmacists doing the paediatric rotation. A total of 5 (9.09%; 95%CI: 3.95-19.58) prescriptions were not finalised by pharmacy or had changes to the prescription after having been validated.

Table 4.20 summarises the number, mean and type of **drugs** prescribed in admission, primary care, during hospital stay and at discharge.

Table 4.20. Drug-therapy variables included in prospective phase in drug chart, primary care, hospital stay and at discharge.

#	Variable	Drug chart	Primary Care	Hospital stay	Discharge CRS
21	Number of drugs	692	674	766	822
	Mean number of drugs ± SD	12.6±4.08*	12.3±4.8*	13.9 ± 3.3*	14 ± 4.4*
	(min,max)	(4,22)	(0,23)	(7, 22)	(3,26)
14	Type of drugs prescribed (%)	N/A	N/A		
	Nebulised mucolytics			100	100
	Anti-reflux drugs			100	96
	Pancreatinin			100	100
	Lipophilic vitamins			100	100
	Nebulised antibiotics			0	78
	Salbutamol inhaled			100	100
	Oral or IV antibiotics			100	87

#: Number of variable; PC: primary care; CRS: Clinical Records System; SD: standard deviation. *ANOVA test, p=0.068.

All *admissions* had **medicines reconciled** within the first 3 days of admission and 52 of them (94.55%; 95%CI: 85.15-98.13) were reconciled with 4 or more sources of information checked, the rest had been reconciled with 3 sources of information. Fifteen different patients, 42.86% (95%CI: 27.98-59.14) had **high cost nebulisers** in the repeat prescription despite repatriation to secondary care completed by January 2015.

4.2.3. Improvement strategies implementation

The following epigraphs relate to the strategies used through patient's admission and hospital stay.

4.2.3.1. Deeper medicines reconciliation during admission.

During admission medicines reconciliation was performed simultaneously on drug chart and on SCR primary care repeat prescription. The following paragraphs show the obtained information:

- There were 39 ***drug charts*** (out of 55 drug charts) with *discrepancies* and 36 (65.45%; 95%CI: 52.25-76.64) drug charts had *non-justified discrepancies (conciliation errors)* in which 473 (68.35%; 95%CI: 64.79-71.71) drugs had been prescribed in the regular side of the drug chart and these corresponded to 26 patients (74.29%; 95%CI: 57.93-85.84). A total of 97 **improvement opportunities** were detected, and 3 (3.09%; 95%CI: 1.06-8.70) of them were non-medication errors whilst 94 (96.91%; 95%CI: 91.30-98-94) drugs of the total of medicines prescribed in the regular side were medication errors.
- From the total of 55 reviewed admissions, a total of 45 **primary care** repeat prescriptions were identified with discrepancies and 39 of them (70.91%; 95%CI: 57.86-81.23) were non-justified in which 477 drugs had been prescribed in the repeat prescription section (70.77%; 95%CI: 67.23-74.08), and these corresponded to 31 (88.57%; 95%CI: 74.05-95.46) patients. The number of **improvement opportunities identified** was 100, of which 15 (15%; 95%CI: 9.31-23.28) were non-

medication errors and 85 (85%; 95%CI: 76.72-90.69) were medication errors prescribed in the repeat prescription in SCR.

The odds ratio value of the proportions of admissions with non-justified discrepancies (ME or conciliation errors) detected in drug charts and in primary care prescriptions (out of 55 admissions) gave a value of 1.29 (95%CI: 0.57-2.88).

In the following Figure 4.5 is represented a diagram with the characteristics of the episodes included in the prospective phase, including the I.O and ME found during reconciliation in the drug chart and SCR (for primary care repeat prescription).

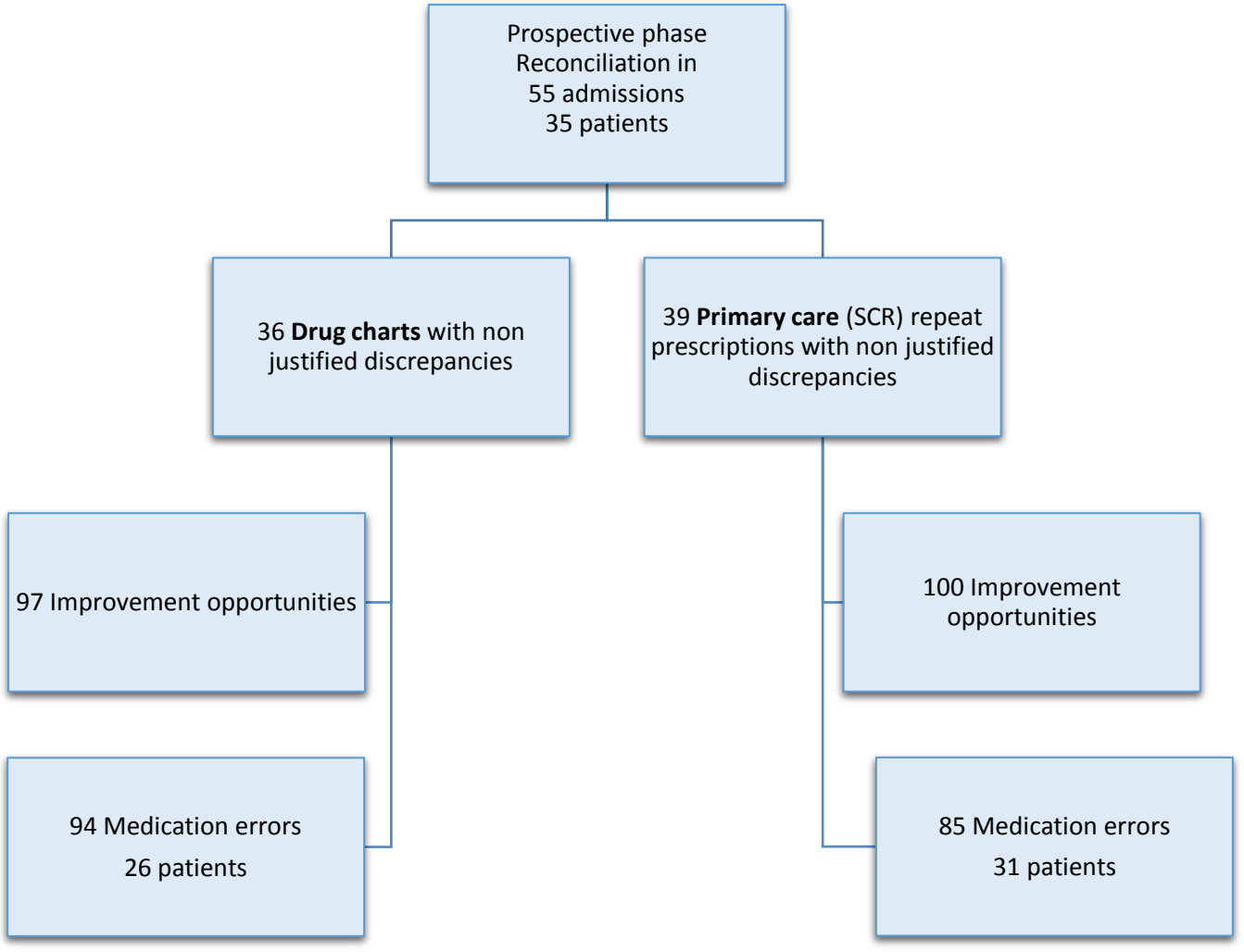


Figure 4.5. Diagram and characteristics of the episodes included in the prospective phase.

The results of the percentages of patient and admissions with improvement opportunities (I.O) during reconciliation in the drug chart and within primary care repeat prescription are summarised in Table 4.21.

Table 4.21. Percentage (95%CI) of patient with improvement opportunities (I.O) and admissions with I.O during the different phases of drug history reconciliation studied prospectively.

#	Drug chart n=55		Primary Care n=55	
	Number, percentage (95%CI) of # with I.O			
Patients	26	74.29 (57.93-85.84)	31	88.57 (74.05-95.46)
Admission	36	65.45 (52.25)	39	70.91 (57.86-81.23)

n: number; I.O: Improvement opportunities; CI95%: confidence interval 95%.

4.2.3.2. Prompt card

All 55 (100%) drug charts had the **prompt chart** attached to the front of the drug chart. All the prompt charts had information of the regular medication the patient was on prior to admission and that had been intentionally omitted for IV therapy.

4.2.3.3. Pharmaceutical interventions

During hospital stay, a total of 766 drugs were prescribed in the regular side of the drug chart, with a mean of 13.9 $\pm$ 3.3 (min 7, max 22) drugs per drug chart. There were 136 **pharmaceutical interventions**, with a mean of 2.5 $\pm$ 1.3 (min 1, max 5) per episode of admission. A total of 134 interventions were accepted (98.53%; 95%CI: 94.80-99.60).

Most of the interventions were corrective followed by preventive and educational. Figure 4.6 represents a summary of the type of interventions. Figure 4.7 shows the results of the corrective interventions categories.

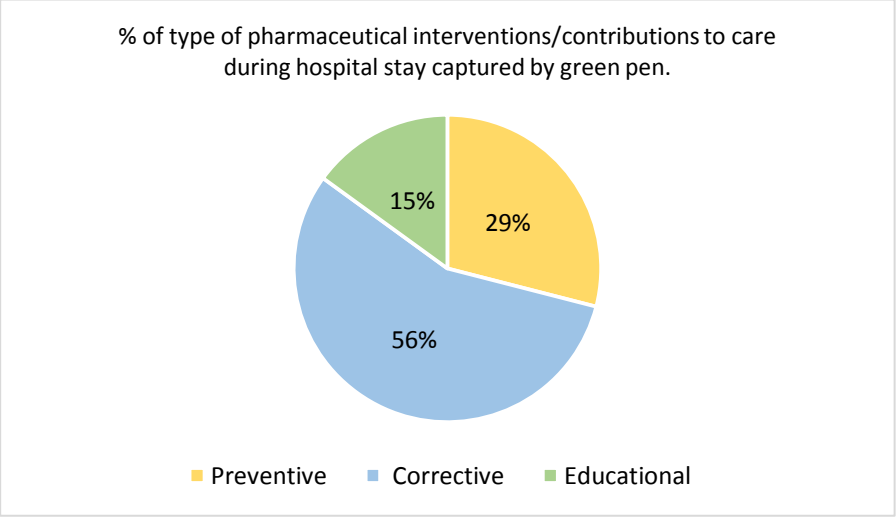


Figure 4.6. Type and % of pharmaceutical interventions performed during hospital stay.

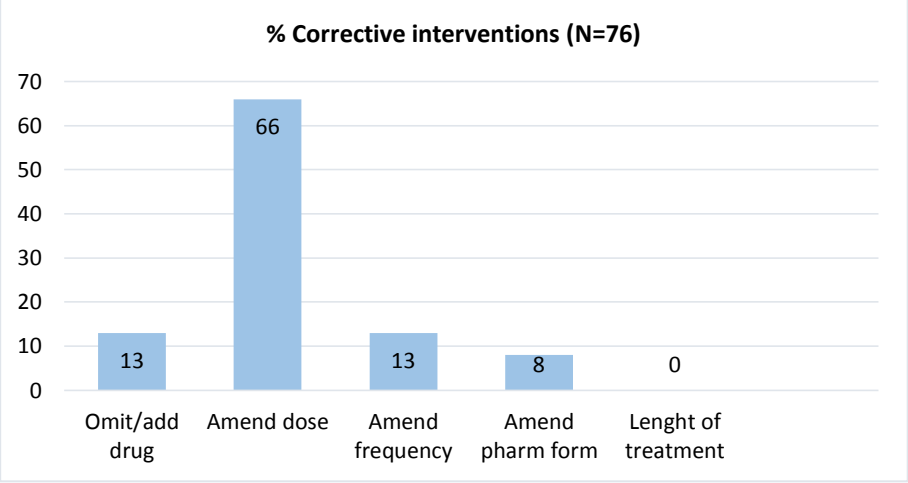


Figure 4.7. Percentage of the corrective interventions categories.

4.2.3.4. Drug listing member of paediatric pharmacy team.

A total of 34 (61.82%; 95%CI: 48.61-73.48) discharges had been either drug-listed or previously reviewed by a **pharmacy technician** prior to pharmacist validation. The total number of drugs reviewed prior to validation was 541.

After pharmacy technician's drug listing or review and pharmacist validation there were:

- 25 (73.53%; 95CI: 56.88-85.40) discharges with the weight present in the final document of discharge and all of them had information about allergies.
- 22 discharges (64.71% (47.91-78.51) with no discrepancies and 12 with discrepancies (35.29%; 95%CI: 21.49-52.09) in which a total of 19 medication errors were found, corresponding to 2.21 ME per 100 drugs listed by a pharmacy technician. The causes of these 12 discharges having discrepancies were mainly technological in 8 of them (66.67%; 95%CI; 39.96-86.19); 1 was educational and 3 were caused by human error.
- 24 (70.59% (95%CI: 53.83-83.17) of the drug listed discharges had information for the GP to update the patient's repeat prescription.

4.2.3.5. Communication

Communication with primary care was needed in mostly all discharges to reinforce either changes or no changes. In 45 different discharges it was needed to amend either allergies or regular medication or both. A total

of 45 (81.82%; 95%CI: 69.67-89.81) of the *discharge* prescriptions had been communicated to primary care regarding changes needed to be amended from that admission as well as conciliation errors noted on admission.

4.2.4. Improvement opportunities.

4.2.4.1. Admission

The results of the rates of the improvement opportunities (I.O) found during drug history reconciliation are presented in Table 4.22.

Table 4.22. Improvement opportunities per patient, admission and 100 drugs prescribed in the drug chart and primary care repeat prescription (SCR) during medicines reconciliation on admission.

I.O found during medicines reconciliation on admission								
		Drug chart				**Primary care repeat prescription (SCR)**		
		Total n	**Non-ME n(%)**	**ME n(%)**		**Total n**	**Non-ME n(%)**	**ME n(%)**
		97	3 (3.1)	94(96.9)		100	15 (15)	85 (85)
#	**IMPROVEMENT OPPORTUNITITES PER #**							
	n	**Total**	**Non-ME**	**ME**	**n**	**Total**	**Non-ME**	**ME**
Patient	35	2.77	0.08	2.69	35	2.86	0.43	2.43
Admission	55	1.76	0.05	1.71	55	1.81	0.27	1.54
100 drugs prescribed	692	14.01	0.4	13.6	674	14.84	2.23	12.61

n: Number; ME: Medication errors; #: case or condition.

As can be seen in Table 4.22, similar rates of ME were detected on admission when comparing both the drug chart and primary care when reconciling the medication with the patient's own drugs and confirming with parents when any clarification was needed.

The following sections present the I.O found in primary care prescription classified by type of admission and by socio demographic variables collected in the prospective phase.

4.2.4.1.1. I.O found in primary care prescriptions classified by type of admission.

Table 4.23 shows the improvement opportunities found in primary care prescription classified by type of admission.

Table 4.23. Improvement opportunities found in primary care prescription classified depending of type of admission.

		Infective exacerbation (n=35)	Elective admission (n=20)	p	Odds Ratio (95% CI)
Repeat prescription in PC with I.O	n	22	17	0.085	3.34 (0.82-13.66)
	%	62.86	85		
	(95%CI)	(46.34-76.83)	(63.96-94.76)		
ME	n	47	38		
ME per PC prescription		2.13	1.9	0.954	1.62 (0.21-12.44)
Drugs prescribed	n	401	291		
ME per 100 drugs prescribed		11.72	13.05	0.599	1.13 (0.72-1.79)

n: Number; % Percentage; 95%CI: 95% confidence interval; PC: primary care repeat prescription; ME: medication errors.

4.2.3.1.2. I.O found in primary care prescription by socio demographics of the patients.

Table 4.24 shows the improvement opportunities found in primary care prescription classified by the socio demographic factors studied prospectively. Table 4.25 shows the p values after applying Chi squared.

Table 4.24. Social analysis of the improvement opportunities found from primary care during medicines reconciliation on admission.

		English of parents as first language (n=55)		Children living with parents (n=55)	
		Yes (n=38)	**No (n=17)**	**Both parents (n=38)**	**One parent (n=17)**
PC with I.O	n	27	12	25	14
	%	71.05	70.59	65.79	82.35
	(95%CI)	(55.24-83.00)	(46.87-86.72)	(49.89-78.79)	(58.97-93.81)
ME	n	50	35	59	26
ME per PC prescription		1.85	2.92	2.36	1.86
Drugs prescribed	n	496	196	503	189
ME per 100 drugs prescribed		10.08	17.86	11.73	13.76

n: Number; PC: primary care; 95%CI: 95% Confidence Interval; ME: Medication errors.

Table 4.25. Statistical analysis with χ^2 of the social variables indicated.

Social variable	**χ^2 p**
English as 1st language (yes/no)	
➢ % prescriptions with of I.O	0.973
➢ ME per prescription	0.804
➢ ME per 100 drugs prescribed	0.005
Children living with parents (both/one)	
➢ % prescriptions with of I.O	0.216
➢ ME per prescription	0.908
➢ ME per 100 drugs prescribed	0.469

The results of the medication errors found during admission in the drug chart and in primary care are described in section 4.2.5, together with the discharge information.

4.2.4.2. Discharge

The discharge prescription (CRS) was evaluated and data was collected withing the first 72 hours of patient's discharge, except in 5 occasions when the prescription was analysed a week after discharge.

The following information resulted after evaluating discharge prescriptions:

- There were 31 (56.36%; 95%CI: 43.27-68.63) discharge prescriptions with I.O containing 452 (54.98%; 95%CI: 51.57-58.36) drugs prescribed. These 31 discharges corresponded to 23 patients. A total of 159 non-justified discrepancies were found, of which 24 (15.09%; 95%CI: 10.36-21.48) were non medication errors and 135 (84.01%; 95%CI: 78.52-89.64) were medication errors.

The percentages of patients with I.O and discharges with I.O are summarised in Table 4.26.

Table 4.26. Percentage (95%CI) of patients with I.O and discharges with I.O.

#	CRS n=55	
	n, percentage (95%CI) of # with I.O	
Patients	23	65.71 (49.15-79.17)
Discharge	31	56.36 (43.27-68.63)

#: Case or condition; n: number; 95%CI: 95 % confidence interval; I.O: improvement opportunities; CRS: computer system used with discharge prescriptions during prospective study.

Table 4.27 summarises the results of the rates of the improvement opportunities (I.O) found in the discharge prescriptions per patient, per

admission and per 100 drugs prescribed during discharge in the prospective phase.

Table 4.27. Improvement opportunities (I.O) found in the discharge prescriptions expressed per patient, per admission and per 100 drugs prescribed during discharge in the prospective study.

IMPROVEMENT OPPORTUNITIES at Discharge (CRS©)				
#		**Total**	**Non-ME**	**ME**
	n (%)	159	24 (15)	135 (85)
		IMPROVEMENT OPPORTUNITITES PER #		
Patient	35	4.54	0.68	3.86
Discharge	55	2.89	0.43	2.46
100 drugs prescribed in CRS	822	19.34	2.9	16.4

#: Case or condition; n: number; ME: Medication error; CRS: computer system used with discharge prescriptions during prospective study.

4.2.4.3. Classification of Improvement opportunities

In order to evaluate the relationship between I.O with pharmacist validation, the discharge day of the week and the socio demographic variables available, the classification of the I.O was performed as per the following sections.

4.2.4.3.1. <u>According to pharmacist validation.</u>

A total of 50 (90.91%; 95%CI: 80.42-96.05) prescriptions were **validated** by pharmacists. A total of 84 **improvement opportunities** were found in 26 prescriptions that contained 383 drugs prescribed and corresponded to 21 patients.

From the 5 (9.09%; 95%CI: 3.95-19.58) prescriptions **not validated** by pharmacists, there were 75 **improvement opportunities** detected and

they were in 5 prescriptions in which 69 drugs were prescribed. This corresponded to 5 patients.

Table 4.28 summarises the number and percentage of the total improvement opportunities (non ME and ME) detected in the discharge prescription when the prescription at discharge was or was not validated by pharmacist.

Table 4.28. Improvement opportunities detected in discharge prescriptions (CRS) classified by pharmacist validation or not validation.

		IMPROVEMENT OPPORTUNITITES		
	n	**Total n**	**Non ME n (%)**	**ME n (%)**
Total		159	24 (15)	135 (85)
Validated by pharmacist	50	84	18 (21.4)	66 (78.6)
Not validated by pharmacist	5	75	6 (8)	69 (92)

n: Number; ME: Medication error.
Note that the number of not validated prescriptions is kept as orientate information, to follow the same pattern as in the retrospective study (despite being as small number).

Table 4.29 summarises the percentage of discharges with I.O in validated and non-validated prescriptions and percentage of drugs prescribed with I.O in validated and non-validated discharges.

Table 4.29. Discharges and drugs prescribed with improvement opportunities found in validated and non-validated discharge prescriptions prospectively.

#	**Validated (n=50)** Drugs prescribed 753		**Non Validated (n=5)** Drugs prescribed 69		**p**
	Percentage (95%CI) of # with I.O				
	n		n		
Discharge	26	52 (38.51-65.20)	5	100 (56.55-100)	0.041
Drugs prescribed	66	9.76 (6.95-11.00)	69	100 (94.73-100)	<0.001

#: case or condition; I.O: improvement opportunities; n: number; 95%CI: 95% confidence interval.

Improvement opportunities were more frequent in non validated discharges ($p<0.05$).

4.2.4.3.2. <u>According to the discharge day of the week.</u>

Table 4.30 represents the discharges, discharges with I.O, drugs prescribed and ME expressed per discharge and per 100 drugs prescribed according to the discharge day of the week.

Moreover, Table 4.31 shows the information from the previous Table 4.30 according to whether pharmacist validation was or was not performed, although the number of children in each category was small when stratifying the groups.

Table 4.30. Distribution of discharges and medication errors classified by day of the week of the discharge.

	Monday-Friday (n=49)	**Saturday-Sunday (n=6)**	**p**
Discharge with I.O n (%)	28 (57.14)	3 (50)	0.742
ME n	110	25	
ME per discharge	3.92	8.33	0.622
Drugs prescribed n	737	85	
ME per 100 drugs prescribed	14.93	29.41	<0.001

Table 4.31. Improvement opportunities detected classified according to pharmacist validation and day of the week.

		Validated discharges (n=50)		Non-Validated discharges (n=5)	
		Monday-Friday	**Saturday-Sunday**	**Monday-Friday**	**Saturday-Sunday**
Discharge	**n**	**46**	**4**	**3**	**2**
Discharge with I.O	**n; % (95%CI)**	25; 54.35 (40.18-67.85)	1; 25 (4.56-69.94)	3; 100 (43.85-100)	2; 100 (34.24-100)
ME	**n**	59	7	51	18
ME per discharge		1.28	1.75	17	9
Drugs prescribed	**n**	698	55	39	30
ME per 100 drugs prescribed		8.45	12.73	130.8	60

n: number; I.O: improvement opportunities; 95%CI: 95% confidence interval; ME: medication error.

No statistically significant differences were found between discharges containing I.O validated and not validated during week days (54.35% vs 100%) and weekend (25% vs 100%).

Due to the limited sample statistically significant differences were not found between the rate of ME detected at discharge during the week (1.28 vs 17, p=0.078) or during the weekend (1.75 vs 9, p=0.702) when the prescriptions had been or had not been validated by pharmacist.

Statistically significant differences were found in the ME expressed per 100 drugs prescribed when prescriptions were or were not validated during the week (8.45 vs 130.8, p<0.001) or during the weekend (12.73 vs 60, p<0.001).

4.2.4.3.3. <u>According to the social factors.</u>

Table 4.32 summarises the discharges, discharges with IO, drugs prescribed and ME expressed per discharge and per 100 drugs prescribed according to **socio demographic** information of admitted patients.

Table 4.32. Socio-demographic analysis of the I.O found at discharge.

	English as first language of parents (n=55)		**Children living with parents (n=55)**	
	Yes (n=38)	**No (n=17)**	**Both parents (n=38)**	**One parent (n=17)**
Discharge with I.O n; % (95%CI)	21; 55.26 (39.71-69.85)	10; 58.82 (36.01-78.39)	21; 55.26 (39.71-69.85)	10; 58.82 (36.01-78.39)
ME n	87	48	95	40
ME per discharge	4.14	4.8	4.52	4
Drugs prescribed n	579	243	598	224
ME per 100 drugs prescribed	15.03	19.75	15.89	17.86

n: number; I.O: improvement opportunities; 95%CI: 95% confidence interval; ME: medication error.

Statistical analysis indicates that medication errors at discharge are not associated with the socio demographics factors assessed (language p=0.096 and parents together p=0.498).

The proportion of ME per discharge did not show statistically significant differences (language p=0.912 and parents together p=0.931).

The proportions of the ME per 100 drugs prescribed at discharge did not show statistically significant differences with regards to the language of the parents or if the children lived with one or both parents, p=0.666 and p=0.857 respectively.

4.2.5. Medication errors detected during reconciliation (on admission) and at discharge.

The next epigraphs show the information relating to ME. In order to ease visualisation of the results ME are presented together on admission and at discharge.

4.2.5.1. Medication errors classified by type and subtype.

To facilitate the results of the medication errors, firstly they are presented by the subtype of committed/omitted errors, and then together with type and subtype. The results presented are the ones found during reconciliation on admission analysing the drug chart and primary care prescription as well as at discharge analysing CRS discharge prescription.

Regarding subtype of medication errors, the percentage of omitted/committed errors during medicines reconciliation on admission

in the drug chart and in primary care and at discharge in CRS are shown in Figure 4.8. The types and subtypes of medication errors are summarised in Table 4.33.

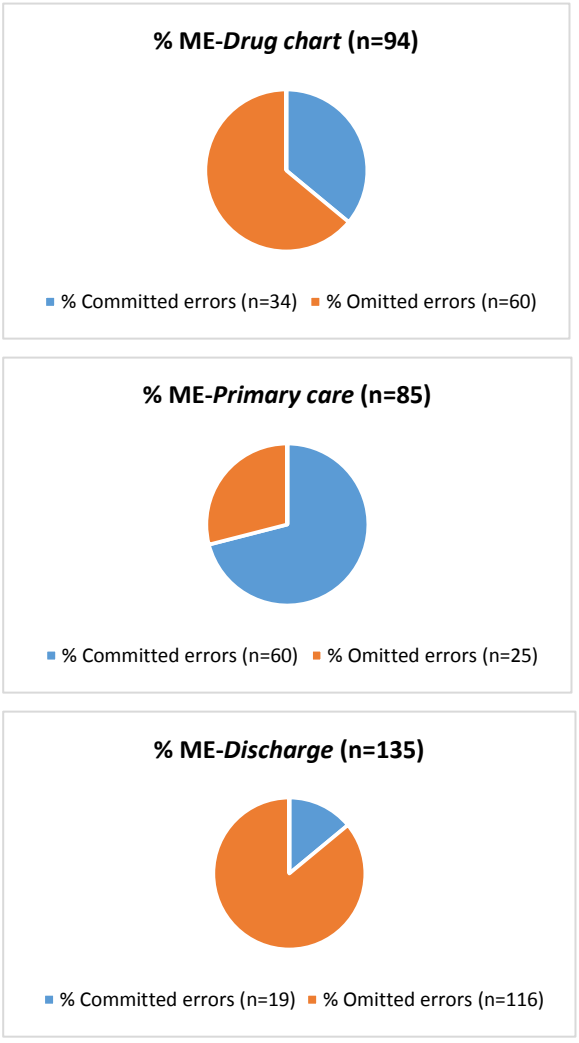


Figure 4.8. Percentage of omitted or committed errors detected in the prospective phase during admission, in primary care and at discharge.

- *Medicines reconciliation on the drug chart during admission and within SCR primary care repeat prescription had the following findings:*
    - The total number of medication errors in the drug chart detected was 94, of which 34 (36.17%; 95%CI: 27.18-46.25) corresponded to committed errors, whilst 60 (63.83%; 95%CI: 53.75-72.82) were omitted drugs. These corresponded to 36 (65.45%; 95%CI: 52.25-76.64) prescriptions and to 26 (74.29%; 95%CI: 57.93-85.84) patients.
    - The total number of medication errors found in primary care was 85, of which 60 (70.59%; 95%CI: 60.18-79.21) were committed errors and 25 (29.41%; 95%CI: 20.79-39.82) omitted. These corresponded to 39 (70.91%; 95%CI: 57.86-81.23) prescriptions and 31 (88.57%; 95%CI: 74.05-95.46) patients.
- At *discharge,* there were 135 medication errors identified, of which 19 (14.07%; 95%CI: 9.20-20.94) were committed errors and 116 (85.93%; 95%CI: 79.06-90.80) were due to omitted information, in which the most common ommission was the route of administration. These medication errors were found in 31 (56.36%; 95%CI: 43.27-68.63) discharges that corresponded to 23 patients.

The following Figure 4.9 summarises information listed above.

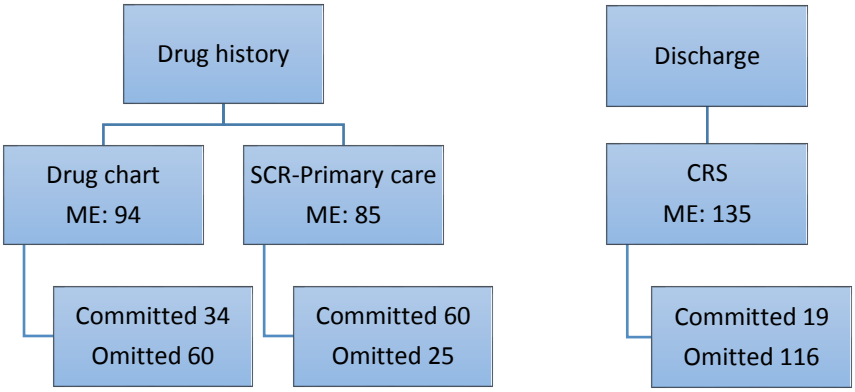


Figure 4.9. Number of medication errors (ME) found in each source of information and indicating the subtype of the ME. Drug history encompasses reconciliation on admission in drug chart and primary care prescription.

The next Figure 4.10 represents the types and subtypes of medication errors detected in each phase studied prospectively.

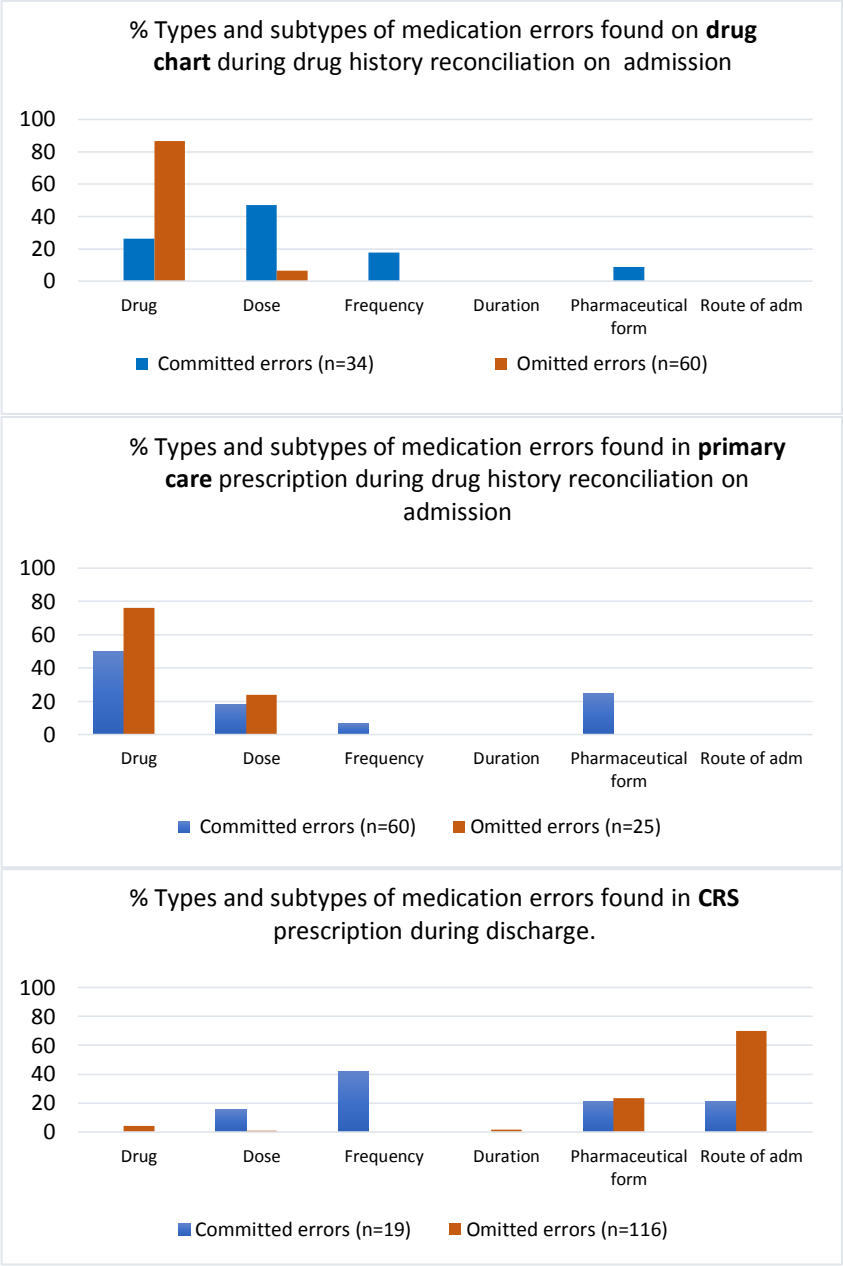


Figure 4.10. Types and subtypes of medication errors detected in each phase studied prospectively.

Below Table 4.33 summarises the types and subtypes of the conciliation errors found during medicines reconciliation within the drug chart on admission and in SCR repeat prescription in primary care, as well as at discharge in CRS prescription.

Table 4.33. Medication errors per category and subtype in different phases of the prospective stage.

			Admission		**Discharge**
		Total n	**Drug chart 94**	**Primary care 85**	**CRS 135**
Committed n / Omitted n			**34/60**	**60/25**	**19/116**
Committed	Drug	n; % (95%CI)	9; 26.47 14.60-43.12	30; 50 37.74-62.26	0; 0 0-16.82
	Dose	n; % (95%CI)	16; 47.06 31.45-63.26	11; 18.33 10.56-29.92	3; 15.79 5.52-37.57
	Frequency	n; % (95%CI)	6; 17.65 8.35-33.51	4; 6.67 2.67-15.93	8; 42.11 23.14-63.72
	Duration	n; % (95%CI)	0; 0 0-10.15	0; 0 0-6.02	0; 0 0-16.82
	Pharm form	n; % (95%CI)	3; 8.82 3.05-22.96	15; 25 15.78-37.23	4; 21.05 8.51-43.33
	Route	n; % (95%CI)	0; 0 0-10.15	0; 0 0-6.02	4; 21.05 8.51-43.33
Omitted	Drug	n; % (95%CI)	52; 86.67 75.83-93.09	19; 76 56.57-88.50	5; 4.31 1.85-9.69
	Dose	n; % (95%CI)	4; 6.67 2.67-15.93	6; 24 11.50-43.43	1; 0.86 0.15-4.72
	Frequency	n; % (95%CI)	0; 0 0-6.02	0; 0 0-13.32	0; 0 0-3.2
	Duration	n; % (95%CI)	0; 0 0-6.02	0; 0 0-13.32	2; 1.72 0.47-6.07
	Pharm form	n; % (95%CI)	4; 6.67 2.67-15.93	0; 0 0-13.32	27; 23.28 16.52-31.75
	Route	n; % (95%CI)	0; 0 0-6.02	0; 0 0-13.32	81; 69.83 60.95-77.43

PC: Primary care; n: Number; CRS: system used for discharge prescriptions during the prospective phase; 95%CI: 95% confidence interval.

4.2.5.2. Causes of medication errors.

Table 4.34 summarises the five main causes of medication errors during admission and at discharge.

Table 4.34. Causes of medication errors detected prospectively classified according to the evaluation time.

		Admission	***Discharge***
Causes of medication errors		Drug chart n= 94 (%)	CRS n=135
Technological	n; % (95%CI)	0; 0 (0-3.93)	121; 89.63 (83.34-93.72)
Organizational	n; % (95%CI)	37; 39.36 (30.09-49.47)	6; 4.44 (2.05-9.36)
Educational	n; % (95%CI)	30; 31.91 (23.36-42.89)	2; 1.48 (0.41-5.24)
Communication	n; % (95%CI)	23; 24.47 (16.89-34.05)	0; 0 (0-2.77)
Human	n; % (95%CI)	4; 4.26 (1.67-10.44)	6; 4.44 (2.05-9.36)

n= number of total errors analysed. Note that in primary care the errors had to be analysed per prescription due to the lack of knowledge of each surgery, general practitioner, etc and the results are not presented.

The primary cause of error on admission was organisational followed by educational whilst at discharge the main cause was technological (nearly 90% of the cause of errors at discharge in the electronic prescription used were technological).

4.2.5.3. Severity.

The following Table 4.35 shows the severity of the medication errors on *admission* and at *discharge.*

Table 4.35. Percentage of ME on admission and at discharge according to the severity.

Severity scale	*Admission*	*Discharge*
Potential severity		
• 1	78	93
• 2	22	7
• 3 or above	0	0

4.2.6. Quality indicators.

Tables 4.36-4.38 show the results defined by the quality indicators described in section 3.10 and whether the Qi value is in line with the compliance standard.

4.2.6.1. Quality of the prescription.

Table 4.36. Quality indicators of the CRS prescription at discharge. Prospective phase

Quality Indicator (Qi)	**Standard value**	**CRS n=55**
Qi 1 (identity)	100	100.00
Qi 2 (weight)	80	65.45
Qi 3 (allergy)	80	90.91
Qi 4 (vitamins in P.I.)	80	100
Qi 5 (P.E.)	80	100
Qi 6 (drug)	90	90.91
Qi 7 (dose)	90	92.73
Qi 8 (frequency)	90	85.45
Qi 9 (pharmaceutical form)	90	74.55
Qi 10 (route)	90	69.09
Qi 11(duration)	90	98.18

n: number; CRS: computer system where the discharge prescription was being written during the prospective phase; P.I.: pancreatic insufficient; P.E: pancreatic enzymes.

4.2.6.2. Quality of the improvement strategies and safety actions.

The evaluation of the quality indicators defined to implement improvement opportunities and safety actions to improve the quality at discharge is summarised in Table 4.37.

Table 4.37. Quality indicators studied to implement safety actions

Safety actions strategies variables studied		
Quality Indicator (Qi)	**Standard value**	**CRS n=55**
Qi 14 (medicines reconciliation)	80	94.55
Qi 15 (prompt card)	80	100
Qi 16 (acceptation of interventions)	80	98.53
Qi 17 (drug listing technician)	60	61.82
Qi 18 (communication with primary care)	80	81.82

n: number; CRS: computer system where the discharge prescription was being written during the prospective phase.

4.2.6.3. Global quality of the paediatric CF prescription.

Table 4.38. Global and standard quality indicators.

Global and standard indicators. Prospective study		
Quality Indicator (Qi)	**Standard value**	**CRS n=55**
Qi 19 global	50	41.82

N: number; CRS: computer system where the discharge prescription was being written during the prospective phase.

The Global quality indicator showed a result of 41.82% of the quality of the prescription at discharge in the prospective phase, around 8 points below the minimal standad value described.

The variables that did achieve the standard value were identity (Qi 1), allergy (Qi 3), vitamins (Qi 4), pancreatic enzymes (Qi 5), drug (Qi 6), dose (Qi 7), duration (Qi 11), medicines reconciliation (Qi 14), acceptation of interventions (Qi 16), and communication (Qi 18). The indicators that did not achieve standard values set in methodology were weight (Qi 2), frequency (Qi 8), pharmaceutical form (Qi 9) and route of administration (Qi 10), which coincide with the majority of the omitted information found with a technological cause of the computer system CRS.

4.3. Improvement analysis in discharge prescriptions.

In order to analyse the quality improvement of the discharge prescription achieved and taking into account **confounding factors** within the prospective study versus the retrospective study, the main characteristics of the variables in each episodes were evaluated.

Table 4.39 summarises the continuous variables for both studies between the two population mean difference and 95%CI.

Table 4.39 Continues variables of the patient and hospital stay comparison with p value.

Variable	Retrospective	Prospective	p
Age (mean ± SD (min-max)	10.5 ± 3.9 (1-17)	10.2 ± 3.9 (2-16)	0.647
Hospital stay (mean ± SD, min-max)	12.8 ± 4.2 (2-22)	13.8 ± 2.4 (6-21)	0.106
Drugs prescribed (mean ± SD, min-max)	13.4 ± 3.9 (6-27)	14 ± 4.4 (3-26)	0.383

SD: standard deviation.

The following Table 4.40 summarises the categorical variables comparison for both studies with the statistical analysis.

Table 4.40. Categorical variables comparison with p value.

Variable		Retrospective	Prospective	P
Gender	male n (%)	31 (31.00)	19 (34.55)	0.652
	female n (%)	69 (69.00)	36 (65.45)	0.652
Associated pathologies	n (%)			
• Pancreatic insufficient		98 (98.00)	51 (92.73)	0.105
• GORD		73 (73.00)	37 (67.27)	0.454
• CF related diabetes		31 (31.00)	16 (29.09)	0.805
• Liver disease/Gallstones		17 (17.00)	18 (32.73)	**0.026**
• Other		53 (53.00)	22 (40.00)	0.122
Reason for admission	n (%)			
• Infective exacerbation		45(45.00)	35 (63.64)	**0.027**
• Elective		55 (55.00)	20 (36.36)	**0.027**
Days of discharge	n (%)			
• Monday-Friday		81 (81.00)	49 (89.09)	0.192
• Saturday-Sunday		19 (19.00)	6(10.91)	0.192

n: number; GORD: gastroesophageal reflux disease.

From all above categorical variables, elective reason of admission and liver disease as associated pathology are the variables showing statistical significance.

The proportion boys/girls for both parts of the study showed statistically significant differences with $p<0.001$ in the retrospective study and $p=0.030$ in the prospective phase.

The number of associated pathologies is shown in the next Figure 4.11 and did not show statistically significant differences ($p>0.05$) between both studies and the distribution of frequencies.

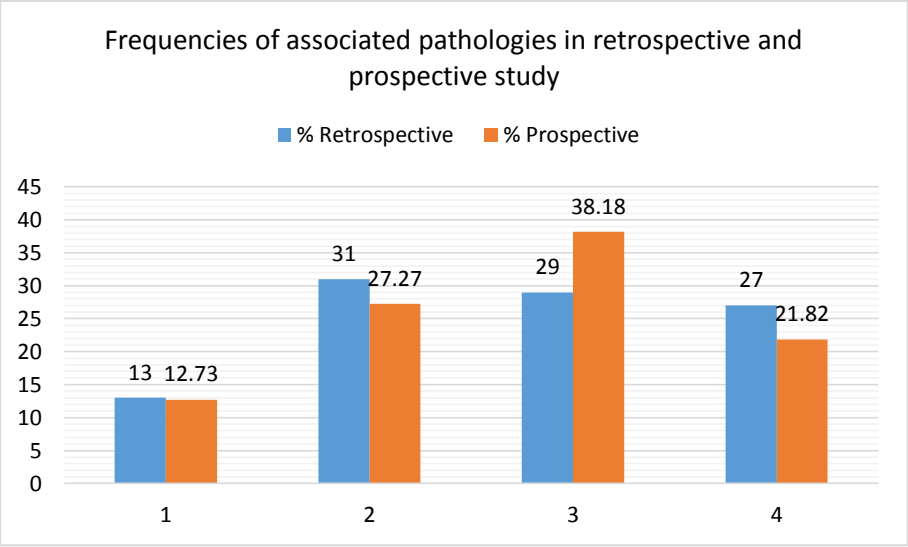


Figure 4.11. Distribution of number of pathologies associated frequencies for both studies.

The following Table 4.41 summarises the comparison of the numerical variables for the proportions of patients with I.O, discharges with I.O and total drugs prescribed with I.O in EPR and CRS, relative risk, estimate 95% confidence interval and p value. Table 4.42 represents the compared rates of I.O per patient, discharge and 100 drugs prescribed between the retro and the prospective phase.

Table 4.41. P values of the percentages of patients and relative risk of the patients, discharges and drugs prescribed with improvement opportunities in EPR and CRS.

#	EPR	CRS	p	RR (95%CI)
	Percentage (95%CI) of # with I.O			
Patients	92.86 (80.99-97.54)	65.71 (49.15-79.17)	0.003	0.71 (0.55-0.92)
Discharge	81.00 (72.22-87.49)	56.36 (43.27-68.63)	0.001	0.69 (0.54-0.89)
Drugs prescribed	12.28 (10.64-14.15)	19.34 (20.17-28.51)	<0.001	1.57 (1.29-1.92)

EPR: Electronic prescription retrospective; CRS: electronic prescription prospective; I.O: improvement opportunities; RR: Relative risk; 95%CI: 95% confidence interval.

The number of patients and discharges with I.O were statistically significantly lower in the electronic prescription system used in the prospective phase (CRS) compared with the one used in the retrospective phase (EPR). However, when analyzing the I.O per 100 drugs prescribed there were more I.O in CRS system, a statistically significant difference.

Table 4.42. Comparison of improvement opportunities expressed per patient, per discharge, and per 100 drugs prescribed.

IMPROVEMENT OPPORTUNITIES							
	EPR			CRS			
	Total (n)	No ME n (%)	ME n (%)	Total (n)	No ME n (%)	ME n (%)	p
	165	17 (10)	148 (90)	159	24 (15)	135 (85)	
	RATE OF IMPROVEMENT OPPORTUNITITES PER #						
#							
Patient	3.93	0.39	3.54	4.54	0.68	3.86	0.895
Discharge	1.65	0.17	1.49	2.89	0.43	2.46	0.607
100 drugs prescribed	12.28	1.23	11.06	19.34	2.9	16.4	<0.001

n: Number; EPR: Electronic prescription report; DL: Discharge letter

Below Table 4.43 represents the comparison of percentages of discharge prescriptions and drugs prescribed that had been validated by pharmacist and had improvement opportunities.

Table 4.43. Comparison of percentages of discharges with I.O in both parts of this study (retrospective, EPR, and prospective, CRS) when the discharges had been validated by pharmacist.

Discharge prescriptions with I.O after pharmacist validation			
	EPR	**CRS**	**P**
#	**Validated N discharges=85**	**Validated N discharges=50**	
	Percentage (95%CI) of # with I.O		
Discharge	81.18 (71.59-88.07)	52.00 (38.51-65.20)	<0.001

There were fewer significantly I.O in discharge prescriptions validated by the pharmacist in the CRS system than in EPR.

The next Table 4.44 represents the comparison between medication errors and their type of errors observed in both parts of this study (retrospective, EPR, and prospective, CRS).

Table 4.44. Comparison of mean number of ME and type of ME in both phases.

Medication error		**EPR N=148**	**CRS N=135**	**P**
Mean ± SD (min, max)		1.48 ± 1.38 (1,7)	4.35 ± 5.27 (1,22)	<0.001
Type of ME				
Drug	N ; % (95%CI)	38 ; 25.68 (19.32-33.27)	5 ; 3.70 (1.59-8.38)	<0.001
Dose	N ; % (95%CI)	35 ; 23.65 (17.52-31.11)	4 ; 2.96 (1.16-7.37)	<0.001
Frequency	N ; % (95%CI)	3 ; 2.03 (0.69-5.79)	8 ; 5.93 (3.03-11.26)	0.091
Duration	N ; % (95%CI)	25 ; 16.89 (11.71-23.75)	2 ; 1.48 (0.4-5.24)	<0.001
Pharm form	N ; % (95%CI)	44 ; 29.73 (22.95-37.53)	31 ; 22.96 (16.68-30.75)	0.198
Route of adm	N ; % (95%CI)	3 ; 2.03 (0.69-5.79)	85 ; 62.96 (54.56-70.64)	<0.001

There were statistically significant differences in the types of errors in 4 of the 6 rights defined. The main subtype of errors is shown below.

Table 4.45 compares the subtype of errors committed/omitted found, with statistical results showing that both subtype of errors were inversely significantly different.

Table 4.45. Comparison of the subtype of errors in both studies and statistical results.

		EPR (N=148)	**CRS (N=135)**	**p**
Committed	N ; % (95%CI)	78 ; 52.70 (44.69-60.58)	19 ; 14.07 (9.2-20.94)	<0.001
Omitted	N ; % (95%CI)	70 ; 47.30 (39.42-55.31)	116 ; 85.93 (79.06-90.8)	<0.001

There were statistically significant differences with both subtypes of errors in the prospective study, with a 6.8 greater probability of finding omitted medication errors in the discharge prescription with CRS than

when the discharge was written in EPR (Odds ratio: 6.80; 95%CI: 3.79-12.18). In contrast, the probability of committed errors to be found in the prospective study were 0.15 times fewer in the prospective study (Odds ratio 0.15; 95%CI: 0.08-0.26).

And finally Figure 4.12 represents the quality indicators used in the discharge episodes (EPR and CRS) in both phases of the study.

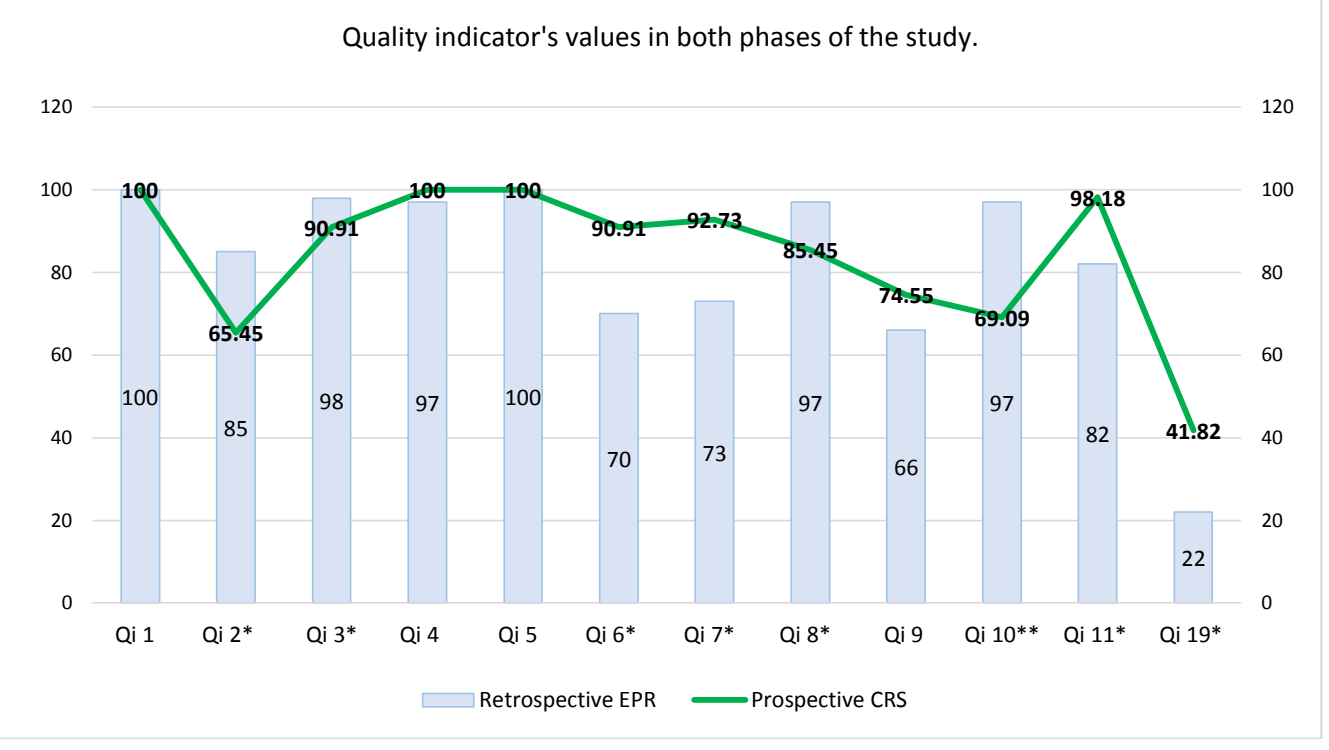


Figure 4.12. Comparison of quality indicators results obtained during the study. Qi: Quality indicator; *: p<0.05; **: p<0.001

5. Discussion

The quality program described could be considered as a monitoring program of the detected medication errors and other improvement opportunities at discharge as well as a study following the effects of a stronger/deeper integration of the pharmacy team in patient's care. The study allowed evaluation of the global quality of the discharge prescription process retrospectively and the quality of the discharge prescription after pharmacist validation prospectively.

The pleasure of this study was seeing the improvement and benefit in the CF department; these findings helping to achieve a better quality and safety of the discharge prescribing in CF children, with the most updated drug history at discharge, despite the limitations of the methodology in this study carried over in tertiary care practice. The standard practice changed slightly the prospective study's development, hence the study is a quasi experimental study.

There were clinical benefits in regards to the identification and prevention of medication errors in children with CF admitted at Barts Health NHS Trust. The study shows different origins of medication errors in different type of prescriptions/medication list: drug chart, primary care repeat prescriptions, and discharge electronic prescription in two different systems as well as a blank word document without existence of mandatory fields to be filled in.

Considering that the patient is at the end of the chain of the prescribing process, when information is not consistent this leads to confusion amongst parents (or GPs) and a potential reduction in adherence to

pharmacological treatment or even incorrect administration of the medication, but also a potential loss of trust of the patient in the prescribers due to queries that need to be solved *a posteriori*.

Medication errors can occur at any stage: prescribing, transcribing, dispensing, drug-administration, with particular risk with the paediatric population due to lack of appropriate paediatric formulation. The inconsistency of the medication errors contained in all analysed prescriptions reflects a possible lack of proactive communication between primary and secondary/tertiary care with a potential impact on the patient, in concordance with *Wong et al' s* investigations regarding communication between health professionals and inadequate clinical practice[154].

Due to the complexity of the prescribing system (or the lack of a unique prescribing system), and the necessity to structure the best medicines optimisation in these high frequency patients coming to hospital for a long stay, it is of special importance to note that the use of unlicensed medication, off label preparations, high cost drugs or medication not approved in certain formularies can lead to confusion, prescribing mistakes and delays of treatment. This could also lead to a patient unaware of being a victim of medication errors. All due to lack of simpler prescribing systems that may have been mainly designed by no clinical experts with a compromised commissioning vision.

As pharmacists are integrated in the multidisciplinary team the evaluation of the medication errors was done after the discharge prescriptions had

been validated by a pharmacist in most of the cases, noting that these errors had not been spotted by the pharmacist validating the prescription. When the patient had left the hospital, with no pharmacist validating the prescriptions, the errors made belonged to junior doctors.

In the prospective phase studied, the improvement strategies were implemented and the figure of the technician was added *a posteriori* as the drug listing role taking was helping the structure of the discharge process. Primary care repeat prescriptions were analysed and the errors found belonged to the GP looking after the patient. It was not possible to analyse the cause of these errors (primary care) although it is likely to be a combination of organisational and educational factors of certain formulations mainly used in CF.

In both phases of the study, the discharge prescriptions were analysed after the final pharmacist validation. The electronic prescriptions investigated in the retrospective phase of the study (EPR) were the control group to evaluate the quality of the process at discharge, as well as to typify the errors and their causes. The discharge letters containing the medication list of the medicines at discharge do not use any prescribing system but are a blank word document. Hence this type of prescribing gives an idea of medication errors when no prescribing fields/guidelines are easily visualised. In the prospective phase, the medication errors were also detected in the primary care repeat prescription and on the drug chart when patients were admitted.

However, the structure of the multidisciplinary CF team is to be applauded, especially the clinical nurse specialists who respond to broad enquiries, solving them and filtering them to the most relevant department when necessary, in which an agreed decision is usually taken by the Consultant. The results of the validation by pharmacist in the discharge prescriptions show reflects the established pharmacy members of the paediatric CF team as the team gains greater experience with this complex disease and individuals. This allows stronger pillars in the CF structure.

5.1. Variables studied.

5.1.1. Patients and hospital stay variables.

All included patients in the study followed inclusive criteria and there were no differences of the population between both studies. The retrospective study was considered as a control group. The number of **patients** being admitted increased as time passed which correlates with the fact that there were 131 patients registered under Barts Health in the paediatric CF database of 2016, in comparison to the number of CF children in 2013-2014, which was 108 (an increase of 21.3%). This was reflected in a higher number of admissions during the prospective study, despite that the covered period did not include the full winter period in the prospective time. This could be related to the CF service being more solid after the major refurbishment of the RLH that finished beginning of

2012. Furthermore, in the last past years the diagnostic technique has become more normalised in different countries and an increasing number of CF patients moving from abroad to the catchment area was noticed.

The mean **age** of the admissions was similar in both parts of this study. Considering that a large proportion of the children included in the retrospective phase were also admitted during the prospective phase electively the age of admissions could have been higher, but in fact the mean age and standard deviation remained very similar in both studies therefore pre-adolescent age was the mean admission age in CF children.

Regarding the **gender** of admissions, during the study it was noted that girls were admitted to hospital more frequently than boys without clinical evidence explaining this fact in CF children. Although the sample might not represent the actual CF population gender ratio, this was discussed with experts whose belief is that girls prior to and during puberty might have a depletion of the immune system causing more girls to be admitted to hospital than boys. Boys normally reach puberty after girls, and boys generally tend to be more physically active than girls. Very little literature has been found to support a general immune system evidence between boys and girls but one study investigated sex-based effects of immunological changes in well trained swimmers and the effect of a maximal incremental swimming task on immunity was shown to be gender dependent and more noticeable in men[155]. Therefore, boys might have stronger immune systems during these years or simply the difference of physically active time or they might have adhered to

treatment for a longer period. Another study evaluated the sex discordance in asthma and wheeze prevalence but no conclusive or relevant information that could relate to this study was found[156]. There is evidence that during puberty (a difficult time for teenagers) there is a potential decrease of adherence in pharmacological treatment[157,158]. No statistically significant differences were found when comparing both phases with the number of admissions per gender, however in each phase of the study there were significant differences in girls admitted to hospital in greater frequency than boys. Further studies would be required to explain why girls were admitted more frequently than boys or whether this occurs in other hospitals or simply that there were a few very sick girls during the time of the study in Barts Health.

All children had at least one **pathology associated** to CF and the most common was pancreatic insufficiency. The hospitalised children in the prospective study had **liver disease** with significant greater frequency compared with the retrospective study (Table 4.40). Although this could be a random cause and shows that both populations in the studies were not homogeneous (only in this aspect), the results of this study should not be affected by this factor. According to the CF Trust website[159] *CF can cause the blockage of small ducts in the liver, leading to liver disease. Although this only happens in about eight per cent of people with cystic fibrosis and can sometimes be managed by drugs, it is a serious health risk and could require a liver transplant.* Possible explanations could relate to liver disease being a natural fact of CF, or to drug induced liver problems

due to the number of drugs patients are exposed to from a young age; but it could simply also be that the department had agreed to share patients with other hospitals that specialise in liver problems. Therefore, further studies are required to understand what could cause a greater frequency of liver disease during the prospective phase or whether this is a random finding, but especially monitor if this might not, potentially, be the beginning of increased cases of liver disease in the studied population.

In regards to the **reason for admission,** the prospective phase of the study showed more hospital admissions due to exacerbations than in the retrospective, and there were significant differences (Table 4.40). As patients were treated the same way, by the same group of professionals and also similar practice such as request microbiology results to adequate best individualised treatment, the only explanation to these findings is random (due to the periods compared 8 months versus 24 months).

UK planned **days of hospital stay** in admissions for elective IV antibiotic therapy in CF patients are normally 14 days, unless the planned admission is for a pre-procedure when the child comes into hospital 3 or 4 days before the procedure and normally these patients are discharged within the first week after procedure. Elective patients' main hospital stay shows two days difference with exacerbations and this indicates that some of the patients are repatriated to their local hospitals to finish the IV treatment or if the parents are trained to give intravenous medications, the patient might go home after multidisciplinary discussion. However, if the admissions are due to an exacerbation, the number of days in hospital

tends to be higher than 14 days. There were no significant statistically differences regarding the mean number of days a patient was hospitalised in both studies (Table 4.39).

Regarding the **discharge days of the week**, elective admissions mostly occurred during week time as the discharge day matches a week day for 14 days of hospitalisation. The results show similar numbers in both parts of the study in admissions during the week and at weekends. In the prospective study, there were fewer discharges during the weekend (10.91%) when compared with the retrospective study (19%) although they were no significant differences (Table 4.40). This lower number of discharges during the weekend indicates that the service tries to avoid discharging at that time of the week as there is not a full respiratory, physiotherapy, dietician and pharmacy service.

5.1.2. Drug-therapy related variables.

Regarding the patient's **weight** in discharge prescriptions, in the retrospective phase this was consistently recorded and this information was found in the multidisciplinary section in EPR, mainly entered by the validating pharmacist. When the weight information was missing in EPR, this information was found in the DL. Only 2 discharges had no records of most recent weight in either EPR or the discharge letter. However, during the prospective phase it was noticed that when the electronic prescription was automatically transferred to the final form, the information of the weight was missing, despite being present in the original CRS prescription designated space for the weight. This was a

technological cause which meant that doctors missing the induction pharmacy talk could be unaware of this fault in the system, unless they are alerted to it. Furthermore, the prompt card had not factored the weight in the points to remember. Although the multidisciplinary team communicates well there are constantly new staff (doctors and pharmacists) that might not be aware of this problem. The results of the proportions of weight documented in the prospective phase of the study showed statistical significance when comparing with the proportions of documented weight in retrospective phase (Figure 4.12, Qi2*, p=0.005) in favour to the retrospective study documenting the weight in higher proportion of prescriptions. During the evaluation of the improvement strategies, weight on admission was recorded in all cases and this was documented on the drug chart. The access to primary care prescription via SCR had no records of the weight of the patient but this does not mean that GPs do not have access to this information, as it might be recorded in another section not accessible in SCR.

The paediatric department has a great culture of **allergies** being checked and documenting them in the appropriate places, and this was shown retrospectively on EPR and although not all allergy status were documented in the DL, all children who had allergies had been documented in the DL. However, during the prospective phase at discharge another problem was noticed with CRS: when allergies were not entered in a specific way in CRS, this information was not transcribed in the final document, unless this information was typed in another free

type section (usually by pharmacy staff), with significant differences (Figure 4.12, Qi 3*, p=0.043). However, when performing medicines reconciliation in a deeper perspective, it was noticed that primary care prescriptions had not updated the most recent allergies in all the children. Although this could be considered a problem, the likelihood of a mistake to occur would be low since the allergies of these CF children were mainly for intravenous presentations, which are rarely dispensed in community. However, due to the risk of real allergies and prescribing, further studies might be relevant for investigation in primary care and hospital for other population with medication allergies that refer to oral drugs taken and that are frequently prescribed in primary care too.

Considering that any concurrent use of 5 or more drugs is polytherapy and concurrent use of 10 or more drugs is excessive polytherapy[160], excessive polytherapy would be the accepted way in which the majority of CF children are treated in the United Kingdom and in other developed countries, regarding the number and **type of drugs**. The common drugs seen prescribed for CF children were consistently written up by the junior doctors in both studies, and these drugs were analysed in groups. *Brown and Bussell* confirm that the treatment of chronic illnesses includes long term use of pharmacotherapy but also note that approximately 50% of patients do not take their medication as prescribed[161]. Although this study does not review patient's adherence, a potential risk of adherence was observed when statistic p value was not too far from being statistically significant between the mean number of drugs prescribed in

different stages of patient's care, including primary care and at discharge with CRS (p=0.068, Table 4.20). A possible justification found by the investigator is that some patients were regularly admitted to hospital for IV therapy and they might just have kept receiving the medication at discharge and patients did not have the necessity to add this to the repeat prescription. Another posible justification was that high cost nebulised medication was taken into account at discharge but these drugs are dispensed via homecare and not through primary care. Although a percentage of patients still had high cost nebulisers in their repeat prescription, this was also taken into account, therefore the possibility of counting more number of medication in one or another prescription should be disregarded for such statistical analysis.

Pancreatic insufficient children must take pancreatinin enzymes and lipophilic vitamins to ensure that fat-soluble nutrients/vitamins are absorbed in the gastrointestinal tract and do not compromise growth. All the children that came to hospital and were discharged home with any pancreatinin enzyme were pancreatic insufficient; the percentage of children who did not have pancreatinin prescribed at discharge corresponded to children who were pancreatic sufficient. The advice on how to take the pancreatinin enzymes was written mainly by pharmacists indicating to take them with meals. Information on taking them also with lipophilic vitamins was not consistent in the majority of the electronic prescriptions. However, this was not studied in detail as this area belongs to a dietician who has a closely monitors the patients. The role of the

dietician in the multidisciplinary team within the CF department is of high importance and children/parents have regular meetings with the dietician from the early diagnosis moments to make sure they understand how to take the pancreatinin enzymes and when to increase or decrease the daily number of doses, helping children and parents to find signs of steatorrhea or potential Distal Intestinal Obstruction Syndrome (DIOS) amongst other educational advice and nutritional input.

Anti-reflux drugs, prokinetics and proton pump inhibitors are part of daily routine medication in CF prescriptions in the UK. Around 95% of the discharge prescriptions (in both parts of the study) contained at least one drug used for the gastrointestinal tract. This high number indicates either over prescribing or the fact that CF children need support with drugs to palliate symptomatology caused by associated pathologies like gastro-oesophagus reflux disease (GORD). It is, however, noted that not all patients had in their records GORD as associated pathology, only around 70% in both parts of the study which can indicate that doctors are treating for reflux but not documenting or considering GORD as an associated pathology.

Nebulised mucolytics are necessary for the majority of children with CF, although it could be thought that small children might not use nebulitic mucolytic nebulised due to the difficulty for them to adhere and induce cough. However, the fact that all patients had nebulised mucolytics written in the prescription shows that the unwell children coming to the hospital are the ones who need to take the drug. Dornase alpha was

correctly prescribed following EU recommendations in children from a certain age and this drug was only not seen in any prescription in small children (less than 6 years old) in the retrospective phase. The prospective phase showed few children under 6 years old on Dornase alpha and this was justified in some cases due to a greater need of improving mucociliar clearance. The mucolytic prescribed in all prescriptions was hypertonic saline, followed by Dornase alpha (combined) and fewer patients had the additional mucolytic N-acetylcysteine, an intravenous pharmaceutical form for nebulise use (unlicensed).

Beta agonists would not be expected to be in the majority part of CF prescriptions as the disease does not require the beta receptors stimulation. However, as the prescriptions analysed belonged to unwell children, this drug (mostly Salbutamol as main beta agonist) is prescribed to avoid any possible bronchoconstriction that hypertonic saline could cause, as well as making sure that after its intake and following physiotherapy, the nebulised antibiotics will penetrate in the lungs in the best possible way. Also, hypertonic saline might cause bronchoconstriction, hence Salbutamol would help reversing any bronchocontruction if this was to occur.

The drugs prescribed as brand names were the expected brand names as per the CF drug guidelines. Hence this information was not considered necessary to be followed up prospectively.

High cost nebulisers (HCN) were repatriated to secondary care by the end of the UK financial year in 2015 as these drugs are considered as Hospital

only drugs/prescriptions and are commissioned by NHS England. This means that HCN should not appear in primary care repeat prescriptions. Notwithstanding, a total of 16 prescriptions from 15 different patients, (42.85%) had high cost nebulisers in the repeat prescription despite repatriation to secondary care completed by March 2015, indicating an opportunity to improve primary care prescribing process too. It was imperative to communicate these findings with the general practitioner directly.

Discharge letters complemented the electronic prescribing in EPR, however in few cases were ready to be given on the same day of discharge. Generally, parents take home the electronic prescription the same day their child is being discharged, together with the new and regular medication. The discharge letters are used as a guide for parents and other future prescribers and they provide more information hence each letter takes longer to finish and as a consequence they are normally posted to their home after the day of discharge. Not all discharge letters were written within the first two days after discharge. As discharge letters were written in a free field not specified for prescriptions and not validated by a pharmacist the results showed a higher opportunity of error.

The study shows that the discharge **prescribing** is taken mostly by junior **doctors** in both studies. The **validation by a pharmacist** in the prospective study shows an increase in the seniority of pharmacists validating the

discharge prescriptions (TTAs), reflecting the favourable results of medication errors captured by the investigator.

5.1.3. Confounding factors.

A confounding variable is a variable other than the independent variable that may affect the dependent variable. As per the type of the study conducted, selection bias, information bias, and confounding were considered to be present to some degree[162]. However, the retrospective data was collected by the same person and the analysis was also performed by the same observer all the time for each patient and each admission. Potential confounding variables were identified at the design of the prospective study to ensure that valid information was collected in order to avoid erroneous conclusions about the relationship between the independent and dependent variables. The unique different act to add in the prospective part was the prompt card, as the other strategies proposed were already existent in a normal ward pharmacist's day. Nevertheless, a closer monitoring was to occur as well as a deeper medicines reconciliation during admission in order to help better communication between tertiary and primary care.

However, the collected results of all variables and the analysis of the discharge electronic prescriptions (CRS) were done by the same person in all cases, hence confounding factors would be minimal for this study.

5.2. Improvement opportunities.

The improvement opportunities looked at the improvement needed within the pharmacy department at discharge. The I.O were studied to help understand pharmacist validation errors not picked up after validating the TTA. However, indirectly medication errors from the prescribers were captured retrospectively in the non-validated EPR prescriptions and from all the DL (although the DL are not per se a formal prescription but a white word document with the list of the medication written on it, which could provide information on number of ME by free typing without using a non standard prescribing system).

EPR showed 2.2 times of less I.O than DL (Figure 4.1). The trend of the I.O in EPR was slowly changing as the prescriptions were studied towards the end of the 2014 in the retrospective phase, likely due to the pharmacist being more exposed to the respiratory ward at that time, and gaining greater seniority. Nevertheless the definition of the retrospective part of the study did not break up the time of data collection.

The percentage of drugs prescribed with I.O were significantly less in validated prescriptions ($p<0.001$, Table 4.8), meaning that the greater the participation of the pharmacist in clinical scenarios the lesser the risk to patients.

Although the discharge letter is extremely comprehensive and useful, omitted information in the discharge letters was found in higher proportion than in EPR. As a consequence the opportunities of error

found in the discharge letters were twice greater than the electronic prescribing. During the retrospective investigation it was also noticed information in some drugs copied and pasted from previous discharge letters and, as a consequence, repeated errors as well as not listing the most updated number of medicines the patients were taking. Another cause for the errors found in DL could be that some junior doctors typed the DL after patient's discharge and it was likely that there was no drug chart against which to compare the medicines taken during hospital stay but also there was no pharmacist input in validating this information in DL.

The **causes** of medication errors were estimated during the retrospective part of the study and the investigator estimated that the greatest causes were, first, the organization of the NHS system and second, educational. Rotational staff stay in the specialist area for 6 months, doctors and rotational junior pharmacists. Doctors move hospitals nationally with different electronic prescribing systems and drug charts lay out. This means they must get used to the process of the prescribing system fast. Therefore, however intense the educative input from the respiratory department is given in CF prescribing, and considering that the essence of prescribing should be the same in any country, still there might be some confusion on the process of prescribing, being then a cause of error. Furthermore, listing the medication in a word document as it was the case for the DL, is a cause of the organizational system since there is no way of prompting to add key information in the prescription like the 6 rights.

Also, junior pharmacists are required to have multiple skills that need are applied to paediatric prescriptions even when the juniors have had limited or nil exposure to paediatrics or the juniors rotating in paediatrics have limited clinical exposure with CF children. Furthermore, the prescribing by junior doctors is not always supervised by consultants but a pharmacist on the wards and pharmacist that validated the majority of the prescriptions during the retrospective phase of the study were junior pharmacists within a rotational post too.

During the prospective stage, I.O were investigated in different steps looking from different angles of the patient's prescribing care. The initial aim was to get a completed drug history on admission and monitor any changes in order to communicate this to primary care at discharge, with an updated accurate prescription at discharge. Therefore primary care prescriptions I.O and the drug chart on admission were studied together, and parent/patient interviews were carried out unobtrusively until a complete and accurate drug history was confirmed. The methods did not include any specific sort of interview of the parents, hence this was not accounted in any specific way for this study and when the investigator felt that the patient could benefit from some education in order to optimise treatment, this was provided in situ or referred to the CF consultant pharmacist. Further studies would be required to follow the trend of a patient's understanding of their disease and adherence to treatment.

Regarding primary care, the number of I.O found in the repeat prescriptions were similar to the ones on the drug chart on admission but

there were more patients with I.O in primary care repeat prescriptions than in the drug chart on admission, however the origins of the medication errors were different (Figure 4.5). This indicates a possible lack of time in primary care surgeries to adapt continuous new treatments or changing treatment/doses in patients that come to hospital frequently.

When the I.O were studied per type of admission, there were no statistical differences, although the elective admissions had greater percentage of primary care repeat prescriptions with I.O in comparison with infective exacerbations (p=0.085, Table 4.23).

In the UK, children with CF from more disadvantaged areas have worse growth and lung function compared with children from more affluent areas[163]. In general, the East London population experience higher than average levels of deprivation with some boroughs ranking 7th most deprived in London and 22nd nationally[164]. Basic **social** aspects that could directly affect patients with medication errors of administration or even understanding of the necessity of good adherence to treatment were studied. In primary care prescriptions, there were no significant statistical differences between the groups of children whose **parents spoke English** as a first language or did; nor between **children living with both parents** or with one parent (and likely to spend the weekends or holidays in another house, with the all the medication transported with them). Despite the number of primary care prescriptions with I.O found in the group of parents with English language as their first language did no show statistical differences, the rate of ME per 100 drugs prescribed were more

frequent when parents did not speak English as their first language (p=0.005, Table 4.25). In regards to the other social aspect studied, the number of primary care prescriptions and I.O and the rate of ME per 100 drugs prescribed did not show any significant differences with children living with one or both parents.

The same two social aspects studied at discharge did not show any significant differences within the same variables mentioned (Table 4.32).

Further studies are required to understand if any of the above social aspects studied can compromise or aid a better adherence to drug treatment and therefore reduce the numbers of admissions as well as helping to control associated pathologies in a more effective manner.

The prospective phase had the advantage of having the figure of a **pharmacy technician** present in the paediatric wards helping the pharmacist to focus on clinical needs. The technician had great knowledge of the computer system and as the technician was ward based, it was easier to identify particular needs for patients (such as especial pharmaceutical forms stock requirements), making the prescribing and validating process smoother. The technician took a role of drug listing with an aim to facilitate the discharge process which helped pharmacists validating the prescriptions by entering the data needed that, as a default, the system was not transcribing to the final document, such as weight, allergies. The service to drug list was only provided when capacity allowed this and despite there being no significant differences, there was a reduction of the percentage of non-validated prescriptions in

the prospective study (from 15% prescriptions not validated to 9.09% of non validated prescriptions in the prospective study, Tables 4.8 and 4.30), likely due to the pharmacy techinician role with prescriptions being listed in a timely manner prior to patient's discharge.

In regards **validated/non-validated prescriptions by pharmacist**, the number of ME found in validated prescriptions was higher retrospectively (Table 4.7) and this could only be due to suggestions not accepted at the time of correcting the prescription or real errors not picked up by the junior pharmacist, mostly dose errors of nebulised colistimethatate. The contrary occurred prospectively (Table 4.28).

I.O after pharmacist validation were found more frequently in the electronic prescriptions in the retrospective part of the study than in the prospective stage ($p<0.001$ Table 4.45). This could be related to the strategies implemented but also that there was an increased number of discharge prescriptions validated by senior pharmacists being exposed to CF cases.

In the retrospective period of the study, the pharmacist validation of the discharge prescriptions did not increase the probability of identifying episodes of I.O and there were no significant difference ($p=0.915$, Table 4.8), but there were in the prospective study ($p=0.041$, Table 4.31). However, when taking as a reference the total number of drugs prescribed, the validated prescription had significantly lesser number of I.O in both phases of the study ($p<0.001$, Table 4.8 and 4.29). This means that the participation of a clinical pharmacist is of relative importance,

since the reduction of medical errors is significant when the prescriptions are validated.

Furthermore, the prospective part showed significant differences when the prescriptions were validated/not validated: when comparing the proportion of discharges with I.O and with the percentage of drugs that had I.O ($p=0.041$ and $p<0.001$ respectively, Table 4.29). These results show greater contribution to safety within the prospective stage. There were no similar publications found to compare these findings.

Nevertheless, it is important to mention that the non-validated samples were small and these numbers calculated might not be fully representative to real scenarios but certainly orientate. In fact the subdivided variable of validated/not validated during the week and the weekend provides orientate information and statistical analysis was not applied due to the lack of homogeneity of the sample.

5.3. Medication errors.

No information was found published regarding medication errors at discharge in paediatric CF patients, hence the expected rate of medication errors was based on studies for paediatrics but most of the literature searched did not contemplate discharge prescriptions or polytherapy. Overall, between 5 to 27% of all paediatric medication prescriptions resulted in a medication error[165,166,167]. Kaushal et al reflected that paediatric inpatients may have three times more medication errors than adult inpatients, and these errors are frequently

harmful. In their publication relating to children, 1% of all medication errors carry significant potential for harm, with 0.24% of errors causing actual harm[166166] and stated that children are at high risk for these errors. Few studies identify the reason that children are at high risk for error is due in part to the need for weight-based dosing[168,169,170.] However, the findings in the present dissertation barely correlate with the literature as in the retrospective phase dosing errors were third on the list after pharmaceutical form and drug errors (table 4.43). In fact, the results in this research show that mostly pharmaceutical form is the consistent medication error in both phases of the study. Therefore formulations or pharmaceutical forms should also be considered in definitions of medication errors. Different reasons to justify this would mainly correspond to either change of therapeutic effects on pharmacokinetics in patients when using different formulations, or previous agreement between professionals and the patients to help adherence as well as the limited paediatric formulations, in which doses might be prescribed in volumes (or parents/carers might get used to the volumes) but different strengths might also be available, as well as when unlicensed use is often prescribed.

In a prospective study of 5 months, *Huynh et al*. evaluated the discrepancies of medicines reconciliation in children at the time of hospital admission finding that 45% of the children had at least one unintentional medication discrepancy. No single source of information provided all the relevant details of a patient's medication history.

Parents/carers provided the most accurate details of a patient's medication history in 81% of cases. It is not surprising that children admitted to hospitals across England are at risk of harm from unintended medication discrepancies at the transition of care from the community to hospital[171].

Therefore CF children, normally on excessive polytherapy, are vulnerable to potential transitional care medication errors, specially due to their low thresold to hospital admission as per CF disease or associated pathologies. In the present study, during **medicines reconciliation** when there were discrepancies these were evaluated (justified or not justified) and medication errors were studied prospectively in order to have accurate information for the following transitional care of the discharge prescription, which could be used reliably as a future reference for the following admission. The most common errors on admission were omitted and continued drugs of medicines not needed due to the new circumstances of the admitted patient, followed by committed dose errors. These errors were corrected in the hospital and when there were community errors in the primary care repeat prescription, they were communicated to primary care. To have a completed accurate reconciliation recorded 4 sources of information were needed in most of the cases, the 4th one being the parents in most of the cases.

Discharge ME found in the retrospective phase were due to incorrect frequency, duration and route being significantly more frequent in EPR than in DL, whilst errors in dose and pharmaceutical form in the DL had

similar percentages in EPR and in DL. In fact, some of the DL took into account regular nebulised antibiotics that had been omitted during discharge prescription, which was linked to the lower errors in duration in the DL which was better explained. Furthermore, there were significant differences in duration errors that supported the presence of DL. DL also gave greater clarity to the parents over when the children would need to restart or stop certain treatments (Table 4.12).

The main ME in EPR were due to committed errors whilst DL mainly had omitted prescribing of the 6 rights, (Table 4.13). This is due to the fact that no computer system was used in DL that would issue a prompt to follow the essential information needed when prescribing.

However, the prospective phase of the study showed a significantly greater rate of medication errors compared with the retrospective study (Tables 4.41, 4.42). After analysing the classification and the cause of error, the prospective study showed that drug, dosing and duration errors were significantly less frequent (Table 4.44) and there was also significant reduction in the subtype of errors committed versus omitted information, being the percentages containing less committed errors in the prospective study ($p<0.001$, Table 4.45). These findings are relevant because if the literature found relating to ME was based on discharge prescriptions, it would contradict some of the evidence which states that incorrect dosing is the most commonly reported error, including computation errors of dosage and dosing interval[172,166].

The advantage of the prospective study was that the committed errors of dose and frequency found were discussed with the prescribers to confirm error and discuss any potential impact and action were taken to rectify them by contacting the parents directly and making sure that the error would not reach the administration stage (as an example, that Azithromycin would not be given three times a day but three times a week, which would be quite unlikely as this was part of their regular medication and parents were well aware of their children's treatment).

The paediatric pharmacy team is known to the CF department and this close relationship permits closer communication and understanding of CF drug therapy needs which is reflected in the way the discharge prescriptions were handled in the latest study. In fact the presence of a pharmacy technician to help on the wards and at discharge was extremely valuable for ensuring accuracy of usual patient's pharmaceutical forms were written down in the discharge prescription as well as getting the discharge medication in an optimised timely manner.

Pharmacist validation of the electronic prescription at discharge showed an inverse proportion of seniority validation during the prospective study: while in the retrospective study 73% of the validations were by junior pharmacist and couple of years later during the prospective study 70% of the validated prescriptions were screened by a senior pharmacist. The rates of ME were not lower prospectively but certainly the type of the ME committed was lower prospectively and this is to be attributed to either the improvement strategies or to the seniority but certainly the

combination of both had an effect when analysing the results of the prescriptions in the prospective study.

The effect of when the prescriptions had been written, whether during the **week or during the weekend,** was studied. During the weekend, the main prescribers were general paediatricians that had not necessarily previously worked with CF children and the pharmacy service is also reduced, with no guarantee of a senior paediatric pharmacist covering the service. The retrospective study showed no significant differences of validated prescriptions during the week or at weekends, although only a small number of discharges were done during the weekend (n=13, Table 4.11), the findings in the non-validated prescriptions during the week and at weekends are small and significantly higher during the week. However, in the prospective study the number of ME detected per 100 prescribed drugs were significantly more frequent in children discharged during the weekend ($p<0.001$, Table 4.30). Again, the influence of the days of the week when the prescription is written with pharmacist validation provide illustrative information as the sample numbers are too small to conclude anything relevant, especially in the prospective study. The non-validated prescriptions during the weekend prospectively would have skipped both, the technician and the senior pharmacist, and either due to the methodology definition of error or due to the computer system not prompting to write the pharmaceutical form or lacking of a unique field for route, the prescribers omitted this information at discharge.

Fortunately the likelihood of causing actual harm with the types of errors found prospectively was minimal since the majority of them were omitted errors at discharge and corresponded to route and pharmaceutical form where patients are used to taking the same medication and are aware of the formulation they prefer. Although it is noticeable that Barts Health has implemented most of the hospital wide system actions and guidelines recommended by the *American Academy of Pediatrics Policy Statement* published by *the Committee on Drugs and on Hospital Care*, it is certainly a challenge to reduce the ME with a computer system that has not been designed for paediatrics and when alert systems are not fully exploited for best use[173].

The **causes** of the ME were mainly technological of the computer system, in fact the odds ratio taking the retrospective study (EPR system) as a reference indicates that it is 82 times of more probable to err in the route of administration when using CRS system in the prospective phase of the study. When prescribing, drug listing or validating, it was difficult to maintain the same standard of the 6 rights for each single line prescribed, especially for route of administration and pharmaceutical forms, which are not mandatory fields to be completed when prescribing. Educational and human error causes were addressed constructively by the investigator with the individuals prescribing, drug listing and validating for future knowledge and reflection. As previously noted, the prospective stage was performed in a different prescribing system which has an important procedural error in the prescribing process.

The potential **severity** of the errors was higher on admission than at discharge and since the CF department has a fluent communication between the team, together with the culture of sharing mistakes, the tendency of these prescribing errors is diminishingover the time because the team is gaining greater experience.

5.4. Quality indicators.

National Institute for Health and Clinical Excellence (NICE) states that the quality indicators are for anyone wanting to improve the quality of health and care services being one of the investigator's intentions. *Smeulers et al.* reviewed literature to identify evidence base quality indicators for safe in hospital medication preparation and administration and although this present study is based on prescribing indicators, the identified quality indicators in this group of investigators was an excellent starting point for developing prescribing specific quality indicators for medication safety. To ensure safe medication preparation and administration, nurses are trained to practice the "7 rights" of medication administration: right patient, right drug, right dose, right time, right route, right reason and right documentation[174]. In parallel in our study, to ensure safe medication prescribing we identified the 6 rights defined in methodology and the actual committed errors or omitted. If our definition of omitted had not been made, the global quality results in the prospective phase would have over achieved the standard value set up. Or in other words, if the

computer system had been designed by a paediatric pharmacist working in Barts Health, the results would show different values.

The standard values of the quality indicators were different depending on the expected quality of the investigator. The 100% value was given exclusively to the indicator for correct patient's identity and this was to make sure that all prescriptions had the correct identity and information of the patient. The 90% standard values were defined for the 6 Rights: drug, dose, frequency, duration, pharmaceutical form and route of administration, permitting a 10% of error. The 80% standard values were given for the nearly the rest of the indicators including allergies and weight since the investigator believed that patients have frequent admissions and most of the allergies were for IV antibiotics that are not prescribed in community, hence discharge prescriptions were allowed a higher margin of error than the 6 rights. The indicator covering drug listing pharmacy technician was given a standard value of 60% due to the service being limited in capacity.

The overall quality indicator had the lowest standard value defined as this indicator viewed all 6 rights correctly prescribed in each drug for each prescription. Considering that there was a 10% allowance of error in each of the 6 rights indicators defined, it was trusted that a 50% of standard value would correspond to a good overall quality of prescription in CF children.

The quality indicators were evaluated in the first phase of the study, retrospectively. The results obtained, together with the change of the

computer system, allowed agreement with the main prescribers to design a prompt card and collect other ideas to implement prospectively, named improvement stategies.

The **strategies implemented** aimed to minimise the error rate at discharge at the same time as having an accurate drug history at discharge prescribed that would be totally reliable for future reference. Hence the quality of the prescription would be consistent with the information. Since the DL were not validated by a pharmacist and in order to provide consistent information to parents and general practitioners as well as to avoid typing the medication list of the patients at discharge in the DL, it was agreed with junior doctors that they would make a **print screen** of the electronic TTA (to take away prescription) of the CRS prescription, and pass this information to the word document of the DL letter. Few random DL were checked at the beginning of the prospective and the doctors had pasted the information from CRS.

In regards to the concept of *in depth* medicines reconciliation, national guidance from NICE, National Patient Safety Agency (NPSA), World Health Organization and the Royal Pharmaceutical Society of Great Britain has long highlighted the importance of accurate and timely medicines reconciliation in reducing medication errors for patients upon transfer of care setting. Current guidance for medicines reconciliation excludes children younger than 16 years old, where widespread use of off-label and unlicensed formulations puts this group of patients at a higher risk[175]. The policy at Barts Health states that reconciliation must be done with at

least 2 sources of information within the first 24 hours of admission. A **deeper drug history medicines reconciliation** was thought to be needed for paediatric CF patients, in order to capture all the high cost nebulisers and prophylactic antibiotics that were stopped during IV therapy and to review them with most recent sensitivities at discharge, as well as reinforcing medicines optimisation and help with adherence. Four sources of information were used in most of the reconciliations and this achieved the standard value stated in the methods which was three. Parents were often interviewed to confirm drug history and identify any potential drug related problems, although this was not a described or defined part of the methodology. In most of the cases it was felt that to do so would obtain full confirmation of prescribing discrepancies found between primary care and labels from patient own medication or documentation from clinics letters or past discharge prescriptions.

The **prompt card** was a home-made tool used to make sure that neither pharmacists nor doctors would forget about the treatment that normally stops during admission but restarts at discharge. Although the initial acceptation of adding the prompt card to the drug chart had a positive participation from doctors filling in the aim date of discharge, as the study was being conducted it was noticed that this field was not filled in, likely due to the persons getting used to this tool and not having any impact on the drug chart.

The figure of the pharmacist is acknowledged in paediatric wards due to the high frequency interaction and contribution to patient's care with

doctors and nurses. This study could not establish an accurate way to count the number of interventions made per day or per patient, as the investigator was based in a different ward when initiating and during the prospective study so direct verbal contribuition to care for CF children by CF pharmacists were not counted. Since the green handwriting is so characteristic of pharmacists, the written interventions were captured. The most common **pharmaceutical interventions** were correcting or amending dosage (corrective); and most of these were dosing not totally optimised or clarifying dotted numbers that could lead to administration mistakes.

The strategy of having a member of the team ward based and providing support to CF discharge prescriptions was initially unplanned for this study, however indirectly this was helping the quality of the prescription and it was included: **drug listing** pharmacy technician. The figure of the technician was created to make sure that CF medication was provided on time at discharge, amongst other tasks. The standard value of the drug listing quality indicator was given a lower value. This was an extra service given only when capacity allowed to spare the technician to drug list them or filter the initial prescription prior to pharmacist validation, as the aim was to minimise waiting time of the patient for their medication at discharge.

It should be noted again that the prospective study had to be performed in a different prescribing system which showed an important procedural error in the prescribing process: routes of administration lack a unique

designated field in the computer system to prompt its prescribing and pharmaceutical form is not mentioned in the system used during the prospective study, hence there is no automatic prompting for prescribers to complete this important information when prescribing and both needed manually entering. Each drug must be typed manually and spelling typographic mistakes were not taken into account as drug errors. The figure of the drug listing pharmacy technician was crucial prospectively to achieve the correct drug formulations written up and the route written next to the drug.

In regards **communication** with primary care at discharge, on some occasions the communication was made over the phone directly with primary care surgeries whilst the patient was in hospital, and although the communication indicator value was achieved in the prospective study, it would be interesting to carry on further investigations to confirm that further information of treatment changes affecting primary care is updated in a timely manner. The investigator kept close contact with the consultant pharmacist informing of specific issues that required special contribution to the individual's care.

Although an overall value of 95-100% for all the safety indicators could have been defined for excellency, the standard values of the quality indicators given were after considering different criteria to achieve quality and safety. The 100% score in correct identity was required. 90% of the correct six rights was thought to be of good quality and safety for our paediatric population. 80% for the rest of the indicators was required,

in which allergies and weight were included here because the investigator considered that there could be room of ommitting since patients have other safety checks and wear distinctive identification tags when they have allergies for instance, plus the dynamics of the allergies in children with CF might vary from one admission to others and parents are well documented. The improvement strategies defined also had a standard value defined of 80% of indicator as the system was complex. A lower standard value indicator of 60% was given to the figure of the pharmacy technician as the drug listing was a service given when capacity allowed and was estimated that due to workload this value of 60% would be the minimum to contribute to quality and safety with the resources available.

The quality indicators of the retrospective prescribing process took into account the administrative analysis of the DL. However, they were not studied prospectively since the doctors agreed that they would copy/paste on the final DL with a **print screen** of the information on CRS corresponding to the discharge, in order to provide consistent information to the parents/patients and to primary care.

The department kept the good quality standards of identity (Qi 1), allergy (Qi 3), prescribing vitamins (Qi 4), and prescribing pancreatin enzymes (Qi 5) in the prospective study. Furthermore the indicators of drug (Qi 6), dose (Qi 7) and duration (Qi 11) improved prospectively achieving the quality standard set up of 90%, being the three of them (drug, dose and duration) significant. Regarding frequency (Qi 8), although maintained to the standard value prospectively the percentage of correct frequency

information prescribed was significantly less than in the retrospective study (97 vs 85.45%, p=0.008). Pharmaceutical form (Qi 9) indicator showed an improvement from the retrospective phase results but did not achieve the standard set up (66% versus 74.55% prospectively).

However, the indicators of weight (Qi 2) and route of administration (Qi 10) showed lesser value in the prospective phase than the achieved value in the retrospective phase. As a consequence, Qi 2 and Qi 10 did not achieve the standard set up of 80 and 90% respectively. Furthermore, the indicator for weight was achieved significantly more frequently in the discharges of the retrospective study. The route of administration (Qi 10) was written up significantly more frequently in the retrospective discharge system (EPR) than in the prospective system (CRS) (97 vs 38%, p=<0.001). This was mostly due to omitted information on CRS. Both indicators of weight and pharmaceutical form/route were caused by the computer system of CRS used in the prospective study. The weight information, for instance, might had been present in the initial prescription but it could not had been translated to the final document, affecting negatively the quality of the prescribing process as well as the quality indicator for excellence at discharge.

The overall quality indicator did not achieve the global standard value defined of 50%, although a significantly greater percentage result was obtained prospectively (p=0.010, Figure 4.12 Qi 19), indicating the team is going in the right direction although there is still room to improve.

However, having a computer system that does not prompt to input information for safe prescribing challenges prescribers and clinical pharmacists in an overloaded work enviroinment. Even so, currently NHS hospitals in crowded areas have times when simply creating a bed space in the hospital becomes a priority. As a consequence discharge prescriptions might be hastily written, which might put junior doctors in situations that they prescribe relying in the pharmacist who validates the prescription. It also compromises the validation in which the pharmacist trusts that a correct reconciliation was performed but with a likelihood of this not being completed when two sources of confirmation had been used whilst checking drug histories in CF children. Further studies should be carried out to ensure the overall quality standard continues to be moving towards the standard defined and that the CF Department is projecting to the deserved excellence due to their continuously daily hard work.

6. Conclusions

This PhD dissertation had as a main objective to improve the quality of the discharge prescription in the paediatric patients with CF that are admitted to receive IV therapy with antibiotics. The following conclusions were yielded:

1. The indicators used to evaluate the quality of the discharge prescription in CF children during the retrospective phase of the study do not achieve the defined quality standard (50%), with greater quality in the electronic prescriptions (22.00%) than the quality found in the discharge letter (9.21%). These value differences highlight the importance of using a prescribing system that integrates specific fields designed to register specific information of the 6 essential parameters of the prescription (drug, dose, frequency, duration, pharmaceutical form and route of administration).
2. In the retrospective phase of the study, the percentage of medication errors (committed and omitted) detected in the electronic prescription at discharge was similar. However, in the discharge letters, the medication errors omitted were detected in greater proportion. The type of medication errors found more frequently in the electronic prescription were due to pharmaceutical form followed by drug and dose, whilst in the discharge letter were due to pharmaceutical form too, followed by dose and route of administration.
3. The contributing factors of medication errors registered in the retrospective phase of the study in the electronic prescribing and in

the discharge letter could be associated to system organisation factors.

4. The improvement strategies implemented after analysing the medication errors and their causes in the retrospective phase of the study were directed to improve the organization of the prescribing process. In the same way as improving the medicines reconciliation on admission and at discharge, as well as improving the pharmacist role in the multidisciplinary team attending the paediatric CF patient.
5. In the prospective phase of the study, the more frequently detected medication errors on admission were due to omitted drugs, followed by incorrect dose. However, at discharge the more frequent medication errors were due to route of administration omission followed by incorrect frequency. In this phase, the main causes contributing to these errors were technological.
6. In the prospective phase of the study, after implementing the improvement recommendations designed, the percentage of discharges with improvement opportunities detected after pharmacist validation shows a significant increase in the quality. There was a reduction of 29.18% in the percentage of improvement opportunities detected in the validation process after patient's discharge (81.18% in the retrospective phase, 52% prospective).
7. Multidisciplinary teams that integrate clinical specialist professionals (doctors and nurses) and specialist in the medication use (pharmacist and pharmacy technicians) facilitate clinical decisions that improve the quality standard in the care of the paediatric patient with CF.

These improvements have an effect in the pharmacotherapy optimisation, in the grade of acceptation of pharmaceutical interventions during hospital stay and all these could contribute to improve the adherence of the patient's pharmacotherapy.

8. The indicators used to evaluate the quality of the prescription in paediatric patients with CF indicate that the implementation of safety actions and improvement strategies designed in this study has contributed to an improvement of the process (22% in the retrospective phase vs 41.82% in the prospective phase). Nevertheless, despite the significant quantified improvement obtained the quality standard (50%) was not achieved. This fact shows the need to strengthen, keep and improve the safety strategies initiated to achieve desired quality quotes/levels.

References

[1] Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989; 245(4922):1066-73.

[2] Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. Science. 1989; 245(4922):1073-80.

[3] Boat TF, Welsh MJ, Beaudet AL. Cystic Fibrosis. In: Scriver CL, Beaudet AL, Sly WS, Valle D, eds. The Metabolic Basis of inherited disease, New York: McGraw-Hill; 1995. p. 2649-80.

[4] Hepler CD, Strand LM. Opportunities and responsabilities in pharmaceutical care. Am J Hosp Pharm 1990 Mar, 47 /93/0: 533-43.

[5] Nurse's Drug Handbook 2009. Jones and Bartlett Publishers, 8th Edition.

[6] Jani YH, Barber N, Wong IC. Paediatric dosing errors before and after electronic prescribing. Qual Saf Health Care. 2010 Aug; 19(4):337-40.

[7] Quinton, P. M. 1999. Physiological basis of cystic fibrosis: a historical perspective. Physiol Rev 79 (1 Suppl):S3-S22.

[8] Bodian HL. Fibrocystic disease of the pancreas. A congenital disorder of mucus production. London, Heinemann W ed.1952:67-146.

[9] Di San't Agnese PA, Darling Rc, Perera GA, Shea E. Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas its clinical significance and relationship to the disease. Pediatrics. 1953; 12(5):549-63.

[10] Bishop HC, Koop CE. Management of meconium ileus, resection, Roux-en Y anastomosis and ileostomy irrigation with pancreatic enzymes. Ann Surg. 1957; 145(3):410-4.

[11] Gibson LE, Cooke RE. A test for concentration of electrolytes in cystic fibrosis using pilocarpine by electrophoresis. Pediatrics. 1959; 23(3):545-9.

[12] Dooley RR, Guilmette F, Leubner H, Patterson PR, Shwachman H, Weil C. Cystic fibrosis of the pancreas with varying degrees of pancreatic insufficiency. AMA J dis child.1956; 92(4):347-68.

[13] Noblett HR. Treatment of uncomplicated meconium ileus by gastrografin enema: a preliminary report. J Pediatr Surg.1969; 4(2):190-7.

[14] Quinton PM. Chloride impermeability in cystic fibrosis.Nature.1983; 301(5899):421-2.

[15] Malena Cohen-Cymberknoh, David Shoseyov, and Eitan Kerem Managing Cystic Fibrosis, American Journal of Respiratory and Critical Care Medicine, Vol. 183, No. 11 (2011), pp. 1463-1471.

[16] Moskowitz SM, Chmiel JF, Sternen DL, Cheng E, Cutting GR. CFTR-related disorders. GeneReviews 2008, Feb 19.

[17] Davies JC, Alton EW, Bush A. Cystic fibrosis. BMJ. 2007 Dec 15; 335(7632):1255-9.

[18] F. Ratjen and G. Döring. Cystic fibrosis. The Lancet, vol. 361, no. 9358, pp. 681–689, 2003.

[19] D. F. McAuley and J. S. Elborn. Cystic fibrosis: basic science. Paediatric Respiratory Reviews, vol. 1, no. 2, pp. 93–100, 2000.

[20] Egan M.E. Genetics of Cystic Fibrosis: Clinical Implications. Clinics in Chest Medicine 37 issue 1 2016. 9-16.

[21] Genetic testing for cystic fibrosis Genetic Testing for Cystic Fibrosis. National Institutes of Health, Consensus Development Conference Statement. April 14–16, 1997. Retrieved on November 20, 2009.

[22] Klimova B, Kuca K, Novotny M, Maresova P. Cystic Fibrosis Revisited-a Review Study. Medicinal Chemistry, 2017; 13(2):102-109.

[23] Cystic Fibrosis Foundation 2008 - Genetic Carrier Testing Updated 07/09/07.

[24] Rosenstein BJ, Cutting GR (April 1998). The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J. Pediatr. 132 (4): 589–95.

[25] Hamosh A, FitzSimmons SC, Macek M, Knowles MR, Rosenstein BJ, Cutting GR (February 1998). Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J. Pediatr. 132 (2): 255–9.

[26] Hytönen M, Patjas M, Vento SI, Kauppi P, Malmberg H, Ylikoski J, Kere J. December 2001. "Cystic fibrosis gene mutations deltaF508 and 394delTT in patients with chronic sinusitis in Finland". *Acta Otolaryngol.* 121 (8): 945–7.

[27] Farrell P. M. The prevalence of cystic fibrosis in the European Union, Journal Cystic Fibrosis 7 (2008) 450-453.

[28] European Medicines Agency document. Orphan drugs and rare disease at a glance. Doc. Ref. EMEA/290072/2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500069805.pdf.

[29] Cystic Fibrosis Trust, What is Cystic Fibrosis? https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs. How common is cystic fibrosis? Webside accessed 2nd November 2016.

[30] Spoonhower K.A, Davis P.B. Epidemiology of Cystic Fibrosis. Clinics in Chest Medicine 37 (2016) 1-8. Elsevier via Athens.

[31] Cystic Fibrosis Foundation. Patient's registry report 2014 (accessed October 23, 2016). Available from: https://www.cff.org/2014-Annual-Data-Report.pdf.

[32] Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007; 29:522–526.

[33] NHS Commissioning board. Clinical Commissioning Policy Ivacaftor for Cystic Fibrosis, March 2012. Reference: NHSCB/A01/P/b. Accessed 2nd November 2016. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf

[34] A. J. A. Duff and G. J. Latchford. Motivational interviewing for adherence problems in cystic fibrosis. Pediatric Pulmonology, vol. 45, no. 3, pp. 211–220, 2010.

[35] Pfeffer PE, Pfeffer JM, Hodson ME. The psychosocial and psychiatric side of cystic fibrosis in adolescents and adults. Journal of Cystic Fibrosis, vol. 2, no. 2, pp. 61–68, 2003.

[36] NHS Screening programme. CF screening algorithm. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397726/Cystic_Fibrosis_Lab_Guide_February_2014_v1.0_12_.pdf.

[37] NHS Screening programme newborn blood spot. Newborn screening for CF. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/411444/CF_clinical_referral_guidelines.pdf.

[38] CF Clinical Guidelines, Royal Brompton NHS Trust, 2014 - 6th edition.

[39] Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK v.2. An Evidence Based Guideline March 2014 Available from: http://www.rcpch.ac.uk/system/files/protected/page/Sweat%20Guideline%20v3%20reformat_2.pdf.

[40] Appendix IX of CF Clinical Guidelines 2014, Royal Brompton NHS Trust, 6th edition.

[41] Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, Kashirskaya N, Munck A, Ratjen F, Sermet-Gaudelus I, Southern KW, Taccetti G, Ulrich G, Wolfe S. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. Journal of Cystic Fibrosis. May 2014, Volume 13, Supplement 1, S23–S42.

[42] Smyth, S. Cystic fibrosis: pharmacological management. Clinical Pharmacist. 1st January 2011.

[43] Makker HK, Holgate ST. The contribution of neurogenic reflexes to hypertonic saline-induced bronchoconstriction in asthma. Journal of Allergy and Clinical Immunology Volume 92, Issue 1, Part 1, July 1993, Pages 82-88.

[44] The British national formulary for children (BNFc) website via medicinescomplete.com, last accessed 31st March 2017.

[45] Hodson ME, McKenzie S, Harms HK, Koch C, Mastella G, Navarro J, Strandvik B. Dornase Alfa in the Treatment of Cystic Fibrosis in Europe: A Report From the Epidemiologic Registry of Cystic Fibrosis.Pediatric Pulmonology 36:427–432 (2003).

[46] England Commissioners mandatory monitoring of parameters in CF patients on Ivacaftor. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf

[47] https://www.england.nhs.uk/wp-content/uploads/2016/12/clin-comm-pol-16049P.pdf. Last accessed 28th March 2017.

[48] Touw DJ. Clinical pharmacokinetics of antimicrobial drugs in cystic fibrosis. Pharmacy World and Science 1998; 20:149–60.

[49] Cheng K, Smyth RL, Govan JR, Doherty C, Winstanley C, Denning N, Heaf DP, van Saene H, Hart CA. Spread of B-lactam resistant Pseudomonas aeruginosa in a cystic fibrosis clinic. Lancet 1996; 348:639–42.

[50] Harrison F. Microbial ecology of the cystic fibrosis lung.Microbiology (2007), 153, 917–923.

[51] Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage and oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatric Pulmonology 1996; 21:267–275.

[52] Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotic therapy for cystic fibrosis. Cochrane Library 2002; issue 3.

[53] Beasley R, Fishwick D, Miles JF, Hendeles L. Preservatives in Nebulizer Solutions: Risks without Benefit. Pharmacotherapy. Volume 18, Issue 1 January-February 1998 (130–139).

[54] McCaffery K, Olver RE, Franklin M, Mukhopadhyay S. Systematic review of anti-staphylococcal therapy in cystic fibrosis. Thorax 1999; 54:380–3.

[55] Weaver LT, Green MG, Nicholson K, Mills J, Heely ME, Kuzemko JA, Austin S, Gregory GA, Dux AE, Davis JA. Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. Archives of Disease in Childhood 1994; 70:84–9.

[56] Antibiotic treatment for cystic fibrosis. Report of the UK CF Trust Antibiotic Group, UK CF Trust, London (2009).

[57] Cigana C, Nicolis E, Pasetto M, Assael BM, Melotti P. Anti-inflammatory effects of azithromycin in cystic fibrosis airway epithelial cells Biochemical and Biophysical Research Communications. Volume 350, Issue 4, 1 December 2006, Pages 977–982. Abstract available in: http://www.sciencedirect.com/science/article/pii/S0006291X06021899

[58] Kosorok MR, Zeng L, West SE, Rock JJ, Splaingard ML, Laxova A, et al. Acceleration of lung disease after Pseudomonas aeruginosa acquisition. Pediatric Pulmonology 2001; 32:277–87.

[59] Stevens DA, Moss RB, Kurup VA, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri R and participants in the CF Foundation Consensus Conference. Allergic bronchopulmonary aspergillosis in cystic fibrosis. State of the art: CF Foundation Consensus Conference. Clinical Infectious Diseases 2003; 37(Suppl 3):S225–64.

[60] Gilbert J, Littlewood JM. Enteric-coated prednisolone in cystic fibrosis [letter]. Lancet 1986; 2:157–8.

[61] Zentler-Munro P, Fitzpatrick WJF, Batten JC, Northfield TC. Effect of intrajejunal acidity on aqueous phase bile acid and liquid concentration in pancreatic steatorrhoea due to cystic fibrosis. Gut 1984; 25:500–7.

[62] Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis Reference: NHS England A01/P/b. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf.

[63] Chorro-Mari V, Christiansen N. Setting up a homecare system for high cost nebulisers in a paediatric cystic fibrosis centre. Arch Dis Child. 2016 Sep; 101(9).

[64] Muller FM, Seidler M Characteristics of pathogenic fungi and antifungal therapy in cystic fibrosis. Expert Review of Anti-infective Therapy Volume 8, 2010 - Issue 8 (957-964).

[65] Nepomuceno IB, Esrig S, Moss RB. Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole. Chest 1999:115; 364–70.

[66] Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, Simpson JL, McElduff P, Gibson PG. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomised controlled trial. Journal of Allergy and Immunology 2003:11; 952–7.

[67] Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. Clin Pharmacokinet. 1998 Dec; 35(6):461-73.

[68] Stevens DA. Managing fungal infections in the 21st century: focus on itraconazole. Drugs 2001; 61 (Suppl 1):1–56.

[69] Bentley S, Gupta A, Balfour-Lynn IM. "Sub-therapeutic itraconazole and voriconazole levels in children with cystic fibrosis". Journal of Cystic Fibrosis. Vol 12, Issue 4, July 2013. 418-19.

[70] Summary of Product Characteristics. Vfend. Available at www.medicines.org.uk (accessed 30 July 2016).

[71] Walsh, T. J., M. O. Karlsson, T. Driscoll, A. G. Arguedas, P. Adamson, X. Saez-Llorens, A. J. Vora, A. C. Arrieta, J. Blumer, I. Lutsar, P. Milligan, and N. Wood. 2004. Pharmacokinetics and safety of intravenous voriconazole in children after single-or multiple-dose administration. Antimicrob. Agents Chemother. 48:2166-2172.

[72] Pasqualotto, A. C., M. Shah, R. Wynn, and D. W. Denning. 2008. Voriconazole plasma monitoring. Arch. Dis. Child. 93:578-581.

[73] Nagappan, V., and S. Deresinki. 2007. Posaconazole: a broad spectrum triazole antifungal agent. Clin. Infect. Dis. 15:1610-1617.

[74] Krishna, G., A. Moton, L. Ma, Medlock MM, McLeod J. 2008. Pharmacokinetics and Absorption of Posaconazole Oral Suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother. March 2009. Vol 53, 3. 958-966.

[75] Krishna, G., M. Martinho, P. Chandrasekar, A. J. Ullmann, and H. Patino. 2007. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy 27:1627-1636.

[76] Summary of Product Characteristics. Sporanox. Available at www.medicines.org.uk (accessed 30 July 2016).

[77] Summary of Product Characteristics. Noxafil. Available at www.medicines.org.uk (accessed 30 July 2016).

[78] Brodzicki J, Trawinska M, Korzon. Frequency, consequences and pharmacological treatment of gastroesophageal reflux in children with cystic fibrosis.Med Sci Monit 2002; 8(7): CR529-537.

[79] MHRA Alert of usage of Domperidone, 18th September 2004. http://www.mhra.gov.uk/home/groups/commsic/documents/drugsafetymessage/con465933.pdf.

[80] Bronstein MN, Sokol RJ, Abman SH, Chatfield BA, Hammond KB, Hambidge KM, Stall CD, Accurso FJ. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. The Journal of Pediatrics. Volume 120, Issue 4, Part 1, April 1992 (533-540).

[81] Cheng K, Ashby D, Smyth R. Ursodeoxycholic acid for cystic fibrosis-related disease.Cochrane Library 2002; issue 2.

[82] Nousia-Arvanitakis, S, Fotoulaki M, Economou H, Xefteri M, Galli-Tsinopoulou A. Long-term prospective study of the effect of ursodeoxycholic acid on cystic fibrosis-related liver disease. Journal of Clinical Gastroenterology 2001; 32:324–8.

[83] National Patient Safety Agency- Rapid Response Report: Safer administration of Insulin, June 2010- Available from http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=74324&type=full&. Accessed 12th November 2016.

[84] Department of Health (2000). *An organisation with a memory. London:* The Stationery Office. Available at: www.doh.gov.uk/orgmemreport/index.htm (November 2003).

[85] Vincent, C, G Neale and M Woloshynowych (2001). 'Adverse Events in British Hospitals: preliminary retrospective record review'. *British Medical Journal*. 322: 517–19.

[86] Aranaz-Andres JM, Aibar-Remon C, Vitaller-Murillo J, Ruiz-Lopez P, Limon-Ramirez R, Terol-Garcia E, ENEAS work group. Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. J Epidemiol Community Health.

[87] Brennan, TA, LL Leape, NM Laird, L Hebert, AR Localio, AG Lawthers, JP Newhouse, PC Weiler, HH Hiatt (1991). 'Incidence of adverse events and negligence in hospitalised patients: results of the Harvard Medical Practice Study I'. *New England Journal of Medicine* 324(6): 370–6.

[88] Leape, LL, TA Brennan, N Laird, AG Lawthers, AR Localio, BA Barnes, L Hebert, JP Newhouse, PC Weiler and H Hiatt (1991). 'The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II'. *New England Journal of Medicine* 324(6): 377–84.

[89] Wilson, RM, WB Runciman, RW Gibberd, BT Harris, L Newby, JD Hamilton (1995). 'The Quality in Australian Healthcare Study'. *Medical Journal of Australia*. 163(9): 458–71.

[90] Coles, J. Pryce, D. Shaw, C. *The reporting of adverse clinical incidents – achieving high quality reporting: The results of a short research study*. CASPE research, October 2001. Found in: www.publichealth.bham.ac.uk.

[91] Ministerio de Sanidad, Politica Social e Igualdad. Plan de Calidad para el Sistema Nacional de Salud: 2010 (citado 6-01-2-15). Available in: http://www.msps.es/organizacion/sns/planCalidadSNS/home.htm.

[92] A Spoonful of Sugar: Medicines Management in NHS Hospitals, 18 December 2001. Available in: http://www.wales.nhs.uk/news/295.

[93] Department of Health NHS, Homecare Medicines Towards a Vision for the Future, November 2011. Available in: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213112/111201-Homecare-Medicines-Towards-a-Vision-for-the-Future2.pdf.

[94] http://www.nhsconfed.org/news/2016/02/carter-review-details-steps-to-up-productivity-and-performance. Last accessed 2nd April 2017.

[95] Item 11 Carter Report October 2016. Implementing the recommendations of Lord Carter's Review of Operational Efficiency. Accessed from *www.lnwh.nhs.uk/EasysiteWeb/getresource.axd?AssetID=8836&type=full.* Last accessed 2nd April 2017.

[96] Reason, J and A Hobbs (eds) (2003). Managing Maintenance Error. A Practical Guide. Hampshire, England: Ashgate Publishing Company.

[97] Reason, J (ed) (1990). Human Error. Cambridge: Cambridge University Press.

[98] Vincent, C (ed), 2001. Clinical Risk Management. Enhancing patient safety. Second Edition. London: British Medical Journal Publishing.

[99] Seven steps to patient safety. Available in http://www.nrls.nhs.uk/resources/collections/seven-steps-to-patient-safety/?entryid45=59787. Last accessed 16th November 2016

[100] Hofer TP, Kerr EM, Hayward RA. What is an error? Eff Clin Pract 2000; 3:1-10.

[101] Hofer T, Hayward RA. Are Bad Outcomes from Questionable Clinical Decisions Preventable medical Errors? A Case of Cascade Iatrogenesis. Ann Intern Med 2002; 137(5): E-327-34.

[102] Leape LL**,** Brennan TA, Laird N, Lawthers AG, Russell Localio A, Barnes BA, Hebert L, Newhouse JP, Weiler PC, Hiatt H. The nature of adverse events in hospitalized patients. Results of the Harvard medical practice study II. N Engl J Med1991; 324:377–84.

[103] Leape LL**,** Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Galivan T, Hallisey R, Ives J, Laird N, Laffel G *et al*. Systems analysis of adverse drug events. JAMA1995; 274:35–43.

[104] Bates DW**,** Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R *et al*. Incidence of adverse drug events and potential adverse drug events: Implications for prevention. JAMA1995; 274:29–34.

[105] Climent C, Font-Noguera I, Poveda-Andres JL, Lopez Briz E, Peiro S. Errores de medicacion en un hospital terciario con tres sistemas de distribucion de mediccamentso ddiferentes. Farm Hosp 2008; 32(1):18-24.

[106] The Nursing and Midwifery Council (NMC) Standards for medicines management 2015.

https://www.nmc.org.uk/globalassets/sitedocuments/standards/nmc-standards-for-medicines-management.pdf Accessed 14th November 2016.

[107] National Reporting and Learning System and national patient safety alert 2016. http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/. Accessed 14th November 2016.

[108] Department of health. The never events 2015/2016. http://www.nth.nhs.uk/content/uploads/2015/05/never-events.pdf. Accessed 14th November 2016 which is currently under consultation in https://improvement.nhs.uk/uploads/documents/NHS_Never_Events_Policy__Framework_Consultation_September_2016_v2.pdf (accessed 14th November 2016).

[109] Manno MS, Hayes DD. How medication reconciliation saves lives. Nursing, 2006.

[110] Marvin V, Kuo S, Poots, Woodcock T, Vaughan L, Bell D. Applying quality improvement methods to address gaps in medicines reconciliation at transfers of care drom an acute UK hospital. BMJ Open 2016 Jun 9; 6(6):e010230.

[111] Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol. 2009 Jun; 67(6): 599–604.

[112] Neale G, Woloshynowych M, Vincent C. Exploring the causes of adverse incidents in NHS hospital practice. J R Soc Med July 2001; (94):322-30.

[113] Mazor KM, Reed GW, Yood RA, Fischer MA, Baril J, Gurwitz JH. Disclosure of Medical Errors. What Factors Influence How Patients Respond. J Gen Intern Med May 2006; (21): 704-10.

[114] Dean B, Schachter M, Vincent, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance, *Qual Saf Health Care* 2002; 11: 340-344 doi:10.1136.

[115] Abdel-Qader DH, Harper L, Cantrill JA, Tully MP. Pharmacists' Interventions in Prescribing Errors at Hospital Discharge: an observational study in the context of an electronic prescribing system in a UK teaching hospital. Drug Safety. November 2010, Volume 33, Issue 11, pp 1027–1044.

[116] Odukoya OK, Stone JA, Chui MA. E-prescribing errors in community pharmacies: exploring consequences and contributing factors. Int J Med Inform. 2014; 83:427-437.

[117] Christiansen SR, Morgan JA, Hilmas E, Shepardson A. Impact of a prescription review program on the accuracy and safety of discharge prescriptions in a pediatric hospital setting. J Pediatr Pharmacol Ther. 2008; 13:226-232.

[118] Gilligan AM, Miller K, Mohney A, Montenegro C, Schwarz J, Warholak TL. Analysis of pharmacists' interventions on electronic versus traditional prescriptions in 2 community pharmacies. Res Social Adm Pharm. 2012; 8: 523-532.

[119] Stasiak P, Afilalo M, Castelino T, Xue X, Colacone A, Soucy N, Dankoff J. Detection and correction of prescription errors by an emergency department pharmacy service. CJEM. 2014; 16:193-206.

[120] Odukoya OK, Stone JA, Chui MA. How do community pharmacies recover from e-prescription errors? Res Social Adm Pharm. 2014; 10:837-852.

[121] Department of Health**.** *An organisation with a memory*. Report of an Expert Group on Learning from Adverse Events in the NHS. London: The Stationery Office, 2000.

[122] The Audit Commission**.** *A spoonful of sugar: medicines management in NHS hospitals*. Wetherby: Audit Commission Publications, 2001.

[123] Reason JT. Human Error. New York: Cambridge University Press; 1990.

[124] Otero-López MJ, Bajo-Bajo A, Maderuelo-Fernández A, Domínguez-Gil A. Evitabilidad de los acontecimientos adversos inducidos por medicamentos detectados en un servicio de urgencias. Rev Clin Esp 1999; 199: 796-805.

[125] Otero-López MJ, Alonso-Hernández P, Maderuelo-Fernández A, Garrido-Corro B, Domínguez-Gil A, Sánchez-Rodríguez A. Acontecimientos adversos prevenibles causados por medicamentos en pacientes hospitalizados. Med Clin (Barc) 2006; 126 (3):81-3.

[126] Finch CH, Self TH. 10 common prescribing errors: how to avoid them. Consultant 2001; 766-71.

[127] Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005; 173 (5): 511-15.

[128] Department of Health. *An Organisation with a memory*. London: The Stationery Office. Available at: www.doh.gov.uk/orgmemreport/index.htm (November 2003).

[129] Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: building a safer health system. Washington, DC: National Academy Press, Institute of Medicine; 1999.

[130] O'Shea E. Factors contributing to medication errors: A literature review. J Clin Nurs 1999 Sept; 8(5):496-504.

[131] Aronson JK. Medication errors: what they are, how they happen and how to avoid them. QJM. 2009 Aug; 102(8):513-21.

[132] Reason, J and A Hobbs (eds) (2003). Managing Maintenance Error. A Practical Guide. Hampshire, England: Ashgate Publishing Company.

[133] White AA, Gallagher TH. After the apology-coping and recovery after errors. Virtual Mentor. AmMed Assoc. 2011; 13(9):593–600. doi:10.1001/virtualmentor.2011.13.9.ccas1-1109.

[134] Hobgood C, Hevia A, Tamayo-Sarver JH, Weiner B, Riviello R. The influence of the causes and contexts of medical errors on emergency medicine residents' responses to their errors: an exploration. Acad Med. 2005 Aug; 80(8):758-64.

[135] Reason J. Human error. Cambridge: Cambridge University, Press 1990.

[136] www.npsa.nhs.uk/rca. Last accessed 18th November 2016.

[137] Care Quality Commission CQC 2016. The fundamental standards http://www.cqc.org.uk/content/fundamental-standards- Accessed 14th November 2016.

[138] NHS Litigation Authority (NHSLA) 2016 http://www.nhsla.com/safety/pages/home.aspx. Accessed 14th November 2016.

[139] Scottish Patient Safety Programme (SPSP) 2016 http://www.scottishpatientsafetyprogramme.scot.nhs.uk/ Driver diagram and change package-Safer medicines document. Accessed 14th November 2016.

[140] 1000 Lives Improving medicines management guideline 2011 www.1000livesplus.wales.nhs.uk/medicines. Accessed 14th November 2016

[141] Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol. 2007 Aug; 59(8):1043-55.

[142] Moss M, Bilbul C, Crook J. Medicines reconciliation for paediatric patients on admission and discharge. Arch Dis Child. 2016 Sep; 101(9).

[143] Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. Qual Saf Health Care 2007 April; 16(2): 116-26.

[144] Ghaleb MA, Barber N, Franklin BD, Wong ICK. What constitutes a prescribing error in paediatrics? Qual Saf Health Care 2005; 14: 352-357.

[145] Individualised treatment recommended for cystic fibrosis patients. The Pharmaceutical Journal, vol 264, N 7083, p242. 12th February 2000.

[146] https://digital.nhs.uk/summary-care-records.

[147] Calidad Farmacoterapeutica, Ed: Jimenez Torres NV et al; Publicacions de la Universitat de Valencia, 2006.

[148] National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) definition of medication error, found in http://www.nccmerp.org/about-medication-errors.

[149] Silverman JB, Stapinski CD, Huber C, Gandhi TK, Churchill W. Computer-based system for preventing adverse drug events. Am J Health Syst Pharm 2004; 61:1599-1603.

[150] Bruce R. Large scale implementation of a medicines reconciliation care bundle in NHS GGC GP practices. BMJ Qual Improv Report 2016;5.

[151] Herbert R. Confidence Interval Calculator (2013). https://www.pedro.org.au/english/downloads/confidence-interval-calculator/. Accessed on 16th February 2017.

[152] https://www.medcalc.org/calc/comparison_of_proportions.php ((to calculate confidence intervals for a mean, the difference between two

means, a proportion or odds, comparisons of two proportions (the absolute risk reduction, number needed to treat, relative risk, relative risk reduction and odds ratio). Last accessed 20th February 2017.

[153] http://www.danielsoper.com/statcalc/calculator.aspx/id=43, for ANOVA test. Last accesed 25th February 2017.

[154] Wong IC, Wong LY, Cranswick NE. Minimising medication errors in children. Arch Dis Child. 2009 Feb; 94(2):161-4.

[155] Morgado JP, Monteiro CP, Matias CN, Alves F, Pessos P, Reis J, Seixas T, Laires MU. Sex-based effects on immune changes induced by a maximal incremental exercise test in well-trained swimmers. J Sports Sci Med. 2014 Sep 1; 13(3):708-14.

[156] Arathimos R, Granell R, Henderson J, Relton CL, Tilling K. Sex discordance in asthma and wheeze prevalence in two longitudinal cohorts. PLOS One. 2017 Apr 25; 12(4).

[157] Bishay LC, Sawicki GS. Strategies to optimize treatment adherence in adolescent patients with cystic fibrosis. Adolesc Health Med Ther. 2016 Oct 21;7: 117-124.

[158] Feiten Tdos S, Flores JS, Farias BL J. Respiratory therapy: a problem among children and adolescents with cystic fibrosis. Bras Pneumol. 2016 Jan-Feb; 42(1):29-34.

[159] https://www.cysticfibrosis.org.uk- last accessed 18th March 2017.

[160] Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc. 2009; Jan 57(1): 82-9.

[161] Brown MT, Bussell JK. Medication adherence: WHO Cares? Mayo Clin Proc 2011 Apr; 88(4): 304-314.

[162] Grimes DA, Schulz K. Bias and causal associations in observational research. The Lancet. Vol 359, Issue 9302, 19 January 2002, 248-252.

[163] Taylor-Robinson DC, Smyth RL, Diggle PJ, Whitehead M. The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. Lancet Respir Med. 2013 Apr; 1(2):121-8.

[164] Barking and Dagenham's community strategy 2013-1016 document accessible in http://moderngov.barking-dagenham.gov.uk/documents/s66226/20130116%20Final%20Draft%20Community%20Strategy.pdf last accessed 18th March 2017.

[165] Cimino MA, Kirschbaum MS, Brodsky L, Shaha SH; Child Health Accountability Initiative. Assessing medication prescribing errors in pediatric intensive care units. Pediatr Crit Care Med. 2004; 5(2):124–132.

[166] Kaushal R, Bates DW, Landrigan C, Mc Kenna KJ, Clapp MD, Federico F, Goldmann DA. Medication errors and adverse drug events in pediatric inpatients. JAMA.2001; 285(16):2114–2120.

[167] Marino BL, Reinhardt K, Eichelberger WJ, Steingard R. Prevalence of errors in a pediatric hospital medication system: implications for error proofing. Outcomes Manag Nurs Pract. 2000; 4(3):129–135.

[168] Barber ND, Batty R, Ridout DA. Predicting the rate of physician-accepted interventions by hospital pharmacists in the United Kingdom. Am J Health Syst Pharm. 1997; 54(4):397–405.

[169] Rinke ML, Bundy DG, Shore AD, Colantuoni E, Morlock LL, Miller MR. Pediatric antidepressant medication errors in a national error reporting database. J Dev Behav Pediatr. 2010; 31(2):129–136.

[170] Rinke ML, Shore AD, Morlock L, Hicks RW, Miller MR. Characteristics of pediatric chemotherapy medication errors in a national error reporting database. Cancer 2007; 110(1):186-195.

[171] Huynh C, Tomlin S, Jani Y. An evaluation of the epidemiology of medication discrepancies and clinical significance of medicines reconciliation in children admitted to hospital. Arch Dis Child. 2016 Jan; 101(1): 67-71.

[172] Crowley E, Williams R, Cousins D. Medication errors in children: a descriptive summary of medication error reports submitted to the United States Pharmacopeia. Curr Ther Res. 2001; 26; 627-640.

[173] Committee on Drugs and Committee on Hospital Care. Prevention of Medication Errors in the Pediatric Inpatient Setting. 2003; 112; 431. Pediatrics.

[174] Smeulers M, Verweii L, Maaskant JM. Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review. PLoS One. 2015; 10(4): e0122695.

[175] Moss M, Bilbul C, Crook J. Medicines reconciliation for paediatric patients on admission and discharge. Arch Dis Child. 2016 Sep; 101(9).