Interventions for the Management of Distal Intestinal Obstruction Syndrome in Cystic Fibrosis.

By
Jessica Ann Green

Keele University

Thesis submitted for the degree of Master of Philosophy:
11th October 2017

Individual Contributions to MPhil

Jessica Green, intercalating medical student: I contributed to the writing and editing for the protocol, "Interventions for the treatment of DIOS in cystic fibrosis". After receiving peer review comments, I was responsible for improving the protocol. I also helped Dr Carroll to edit the protocol, "Interventions for the prevention of DIOS in the cystic fibrosis". I was the main source of correspondence with our Cochrane Review Group (CRG) in order to improve the protocols.

I attended the full, 4-part Cochrane review author course in Oxford in order to gain an understanding of the methodology involved in a Cochrane review and how to navigate the software required for writing a review (RevMan®). I ran the database and registry searches for the Cochrane review and imported the results to an online software program called Covidence©. I then screened all the titles and abstracts for initial inclusion or exclusion, then performed a full-text review for potentially included studies. I performed data collection and data extraction and entered the extracted data to the Cochrane Review software, RevMan®. With help from our CRG, I ran the data through the appropriate statistical analysis. I also performed a Cochrane Risk of Bias assessment for the data. I used the GRADE software to assess the evidence and present the main results in a Summary of Findings table.

I helped to create the proposal for another Cochrane review, to be hopefully undertaken by another MPhil student.

For the survey on the UK practice of the management of constipation and DIOS, I helped to edit the format and structure of the questionnaire on the web-based software program, Qualtrics©. I was also responsible for creating a list of correspondents,

individually emailing them with a web-link to the survey and sending reminder emails one week later. I collected the survey results, presented individual responses to each question on a spreadsheet and calculated the percentages for each response.

Francis Gilchrist, consultant respiratory paediatrician, based at the University Hospital of North Midlands: Dr Gilchrist decided on the thesis subject and had drafted one of the protocols (interventions for the treatment of DIOS) before the start of the academic year. He also attended the Cochrane training course in Oxford. He acted as the external arbiter to resolve disagreements (see Results section in Chapter 4) between WC and I for data extraction and risk of bias assessment. Dr Gilchrist decided that we should undertake the survey and helped me to navigate the online software (Qualtrics©) used to produce it. Dr Gilchrist and Dr Carroll conceived the clinical patients that appeared in the survey questions and allowed me to use their consultant email contacts. After I collected and summarised the survey data, Dr Gilchrist used online software (STATA) for statistical analysis and graphical presentation of the results.

Will Carroll, consultant respiratory paediatrician, based at the University Hospital of North Midlands: Dr Carroll had drafted the protocol (interventions for the prevention of DIOS) before the academic year started. I helped him to address the peer review comments in the protocol. After the protocol was published, Dr Carroll was the second reviewer to independently screen studies for the review. He also checked my data extraction results and risk of bias assessment results against his own before we discussed and resolved any disagreements (Chapter 4).

Nikki Janke, Managing editor at Cochrane: Nikki gave me feedback for my work on the protocols and provided valuable advice about various areas of methodology involved in the review. She also referred me to a statistician regarding the appropriate type of data analysis to use in the review.

Natalie Hall, Cochrane information specialist: Natalie produced a search strategy for the review and gave me advice about importing the search results from certain online registries (WHO ICTRP and ISRCTN).

Sarah Nevitt, Cochrane statistician: Sarah advised me on the correct statistical analysis method to use for the study (Generic Inverse Variance) and advised me how to report results that were not measured in a standardised way (i.e. not continuous or dichotomous).

I am responsible for the presentation, demonstration, explanation and discussion of the findings in this thesis, but I also received guidance and feedback for my writing from Dr Gilchrist. For the systematic review, I received advice and guidance from my supervisors (Dr Gilchrist and Dr Carroll), Nikki Janke (managing editor of the CRG), Natalie Hall (Cochrane information specialist) and Sarah Nevitt (statistician).

Acknowledgements

I would like to thank my lead supervisor, Dr Francis Gilchrist, for his continuous encouragement, expert guidance and incredible support throughout this year. I am grateful for his dedication and for his comprehensive feedback on the drafts of my thesis. I would also like to thank my co-supervisor, Dr Will Carroll, for imparting his vast clinical and statistical knowledge and general words of wisdom throughout the year. He was always on hand to offer his assistance with great enthusiasm and witty anecdotes.

My supervisors have not only given me the confidence to undertake future research, but they have both inspired me to pursue a career in paediatrics.

I am very grateful to Nikki Janke, the managing editor from the Cochrane Review Group, for guiding me through all aspects of the review and offering her expert advice. Embarking on my first Cochrane review was daunting at times, but Nikki was very patient and answered any questions I had. I would also like to thank Natalie Hall, our Cochrane information specialist, for her guidance with the search strategies, navigating the medical databases and collecting data. In addition, I am thankful to Sarah Nevitt, the statistician from the Cochrane Review Group, for advising me on how to analyse the data in the review.

I wish to show my appreciation to the Cystic Fibrosis and Genetic Disorders Review Group for their comprehensive peer review comments on the protocols and for allowing me to undertake the Cochrane review. I am also appreciative to the Cochrane Collaboration for permitting me to attend the training courses in Oxford. The lecturers were engaging, informative and they provided me with the tools to write a Cochrane review.

I am very grateful for being welcomed so warmly to the cystic fibrosis clinics by the whole of the Paediatric cystic fibrosis team at the University Hospital of North Midlands. The team were very approachable and taught me a great deal about the multi-disciplinary management of cystic fibrosis. I would also like to thank the parents and children who attended the clinic, for kindly permitting me to sit in on the consultations.

I greatly appreciate the Research Institute of Primary Care and Health Sciences at Keele and Keele Medical School for allowing me to intercalate. Zara Richards especially helped me to organise the paperwork and admin matters for my MPhil. I am also grateful to Dr Sam Hider for meeting with me to discuss my academic progress on my thesis. Thanks also to Steven Parton at Keele Library for his guidance on searching medical databases.

Lastly, I wish to acknowledge my family and friends for their support throughout my intercalation. My parents require special recognition for supporting me in everything I do and giving me the confidence to pursue my aspirations. I dedicate this thesis to my grandfather, who passed away suddenly at the beginning of the academic year. He was a very intelligent man who valued academia and I know that he would have been proud of my hard work.

Abstract

Distal intestinal obstruction syndrome (DIOS) is a major gastrointestinal complication in cystic fibrosis (CF). It arises when thick mucus and viscid faecal material combine in the bowel, commonly at the terminal ileum or caecum, leading to partial obstruction (incomplete DIOS) or complete obstruction (complete DIOS). There is limited evidence for the efficacy and safety of laxatives used to manage DIOS and insufficient knowledge of current practices used to treat it; consequently, this thesis aimed to evaluate these matters in children and adults.

A Cochrane review was conducted to evaluate the effectiveness and safety of laxatives used for the prevention of DIOS. Of 2631 studies identified, only 1 study was included so meta-analysis could not be performed. The study was a double-blind, placebo-controlled, crossover trial investigating the efficacy of cisapride (a prokinetic drug) in 17 patients with a history of DIOS. Radiograph scores revealed no difference between cisapride and placebo. There were no adverse effects. However, total gastrointestinal symptom scores favoured cisapride with a mean difference of -7.60(95% CI -14.73 to -0.47). However, cisapride is no longer licenced due to cardiac side effects, limiting its clinical applicability.

A quantitative survey was conducted to establish the current treatments for constipation and DIOS in UK CF centres. Results varied greatly, especially for the treatment of DIOS: incomplete DIOS had 23 different 1st line combinations in adults and 22 in children;

complete DIOS had 25 1st line combinations in adults and 17 in children. Over 99% respondents recognised limited evidence for their treatment decisions.

This thesis demonstrates that there is a lack of evidence for the prevention of DIOS and little consensus for the treatment of DIOS, highlighting a need for research, which at present is pitifully lacking.

List of abbreviated persons:

JG: Jessica Green, author of thesis and intercalating medical student

FG: Dr Francis Gilchrist, lead supervisor and consultant respiratory paediatrician

NH: Natalie Hall, Cochrane information specialist

NJ: Nikki Janke, Managing editor at Cochrane

WC: Dr Will Carroll, co-supervisor and consultant respiratory paediatrician

List of abbreviations:

ASL: Airway Surface Liquid

BAL: Broncho-alveolar lavage

CF: Cystic fibrosis

CFRD: Cystic fibrosis Related Diabetes

CFTR: Cystic Fibrosis Transmembrane Regulator

CI: Confidence Interval

CRG: Cochrane Review Group

CT: Computed Tomography

DIOS: Distal Intestinal Obstruction Syndrome

ENaC: Epithelial Sodium channel

ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition

GIV: Generic Inverse Variance

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

ISRCTN: International Standard Randomised Controlled Trials Number.

MD: Mean Difference

MDT: Multi-disciplinary team

MECIR: Methodological Expectations for Cochrane Intervention Reviews

MeSH: Medical Subject Headings

MI: Meconium ileus

MIE: Meconium Ileus Equivalent

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

PICOS: Participants, Intervention, Comparison, Outcomes, Study design

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

RCT: Randomised Controlled Trial

RD: Risk Difference

RevMan®: Review Manager 5.3

RR: Risk ratio

SD: Standard Deviation

SMD: Standard Mean Difference

SE: Standard Error

UK: United Kingdom

WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

TABLE OF CONTENTS

List of Tables:

List of Figures

List of Appendices

Chapter 1: Aims and Objectives

1.1 Overview

This section describes the aims and objectives for this thesis. Chapter 2 provides an overview of the clinical aspects of cystic fibrosis (CF) and the present management of Distal Intestinal Obstruction Syndrome (DIOS).

1.2 Aim

This thesis aims to evaluate the effectiveness, safety and current practice of different laxative agents in the management of DIOS, (complete and incomplete) both in children and in adults with CF.

1.3 Objectives

1. Conduct a Cochrane systematic review to assess the evidence base for the management of distal intestinal obstruction syndrome in cystic fibrosis, on one or both of the following subjects:

   i.) Interventions for preventing distal intestinal obstruction syndrome in cystic fibrosis.

   ii.) Interventions for treating distal intestinal obstruction syndrome in cystic fibrosis.

2. Conduct a survey that investigates the current treatments for constipation and DIOS used in children and adults with cystic fibrosis across the UK.

Chapter 2: Background of Cystic Fibrosis

2.1 Overview

This chapter provides information on CF, focussing on its epidemiology, historical background, aetiology, pathophysiology, diagnosis, clinical features, treatments and includes a brief section on emerging therapies. Distal intestinal obstruction syndrome, the main subject of this thesis, will also be discussed in detail later in this chapter.

2.2 Introduction

CF is an autosomal recessive, chronic, progressive disease in which the sufferer is born with a mutation in the gene encoding the Cystic Fibrosis Trans-membrane Regulator Protein (CFTR). Normally, this protein translates into an ion channel responsible for the movement of anions (notably chloride ions and thiocyanate ions) out of epithelial cells, which keeps the equilibrium of the positively charged sodium ions and water on the epithelial cell surface. An absence or mutation in the CFTR protein results in the build up of thick, sticky mucus in body organs where the protein is found, particularly in the lungs, pancreas, gastrointestinal tract and in the vas deferens in males.

Lung disease causes most of the morbidity and mortality in patients, but other important complications include pancreatic insufficiency, disturbances in gastrointestinal function, nutritional deficiencies and reproductive issues (1). These result in a reduced quality of life. However, not all CF patients will be affected in the same way. Different genetic mutations may present with different phenotypic severities; however, patients with the

same mutation may also present differently due to other factors, such as gene/gene and gene/environmental interactions. This will be discussed in more detail in section 2.5.3.

2.3 Historical Background

It is believed that CF arose between 4000 and 5000 years ago (2), although it was not well documented until the mid-17th century. In an era when supernatural forces were blamed for diseases, CF sufferers were thought by many to be cursed. The common mode of diagnosis was to taste the sweat from the child's forehead, and if discernibly salty, it would predict the child's death (3).

There was very little progress in CF until the 20th century. However, the oldest scientific record of the disease dates back to 1838. This was a post-mortem report by Austrian pathologist, Carl Rokitansky, who conducted an autopsy on an infant with meconium peritonitis. Then, in 1905, Karl Landsteiner discovered meconium ileus and put together the first report, which suggested that the histological changes in the pancreas could affect the digestion of the meconium, hence leading to bowel obstruction (2,4).

Before the mid- 20th century, the disease was not known as CF. In 1888, Samuel Gee, a London physician, titled it "the coeliac affection". He described it as a "chronic indigestion" with stools being "pale in colour, as if devoid of bile**"** (5,4). Scientists eventually discovered that coeliac disease and CF (or mucoviscidosis, an earlier name for CF) were distinctly different in their pathophysiology. This was thanks to further studies conducted in the 1900s, one of the most notable from the paediatric pathologist, Dorothy Anderson, in 1938. Anderson observed that a few patients, who had seemingly responded to their treatment for coeliac disease, lacked healthy pancreatic tissue on

post-mortem examination. She therefore speculated that there was a different kind of pathophysiology occurring in these patients (6**).** The paper was entitled “Cystic Fibrosis of the Pancreas and its relation to Coeliac Disease” and it crystallized our understanding of CF (4).

In 1953 there was a significant breakthrough made by Dr Paul di Sant’Agnese, who revealed the phenomenon of salt loss in the sweat of patients with CF. He discovered this during the heat wave of New York in 1948, where he found that his CF patients became especially salt-depleted (7). Thereafter, tasting the sweat of patients was no longer carried out. A new mode of diagnosis (as we know it today) was developed: the sweat test (see diagnosis section below).

Throughout the mid 20th century, the number of care centres for CF grew in number, as did CF research. Due to the expansion of CF care, a patient registry was launched to gather information about CF patients (8).

The cause of CF became an important focus. In 1989 a group of scientists discovered the most common genetic mutation causing CF to be “a loss of phenylalanine residue at amino acid position 508”; they also discovered the defective protein associated with the gene, CFTR (9). This critical finding enabled scientists to understand more about the aetiology of CF and paved the way for the development of CF-specific drugs in the 1990s. Examples of these include the development of recombinant human DNase (to break down or thin the thickened mucus in the lungs) and a new preparation of tobramycin for inhalation (4).

As the understanding of genetics in CF expanded in the early 2000s, so did the number of drugs available for treatment. The Food and Drug Administration (FDA) has recently

approved a new medication called Ivacaftor, which has been approved for a number of mutations in CF; this will be discussed in more detail later in this review (10).

2.4 Epidemiology

Although it is a recessive condition, CF is still the commonest, life-limiting, genetically inherited disease found in white populations (11). Approximately 1 in 25 of the UK population are carriers of the faulty CFTR gene. The incidence of CF within the UK is around 1 in 2500 births. According to the most recent figures available in the CF annual data report in 2015, there are over 10,800 people in the UK currently living with CF.

The percentage of males with CF is slightly higher than females (53% compared to 47%) and predominantly affects the white population; over 90% of individuals with CF are white. (8)

There has been a persistent yearly increase in the number of adults with CF since the 1980s, from 29.2% in 1986 to 51.6% in 2015. In contrast, the number of children with CF has remained stable. The increase in adults is likely to be due to increased life expectancy as a result of greatly improved management of CF since the 1980s; this means that more children are progressing to adulthood. Children are usually diagnosed in one of three ways: at birth with meconium ileus, detection through newborn screening or presenting with failure to thrive and/or chronic infections. The number of children has most likely remained stable because newborn screening (described in more detail in 2.7.2) has decreased the age at diagnosis. Furthermore, parents who are aware of their carrier

status they may choose to go down the route of pre-implantation genetic screening, or terminate the pregnancy.

2.5 Aetiology

2.5.1 The CFTR protein

CF is caused by a genetic mutation in the CFTR protein. CFTR is a very large gene, located on the long arm of chromosome 7 (7q31) and comprises 27 exons (12).

The protein works as an ATP (adenosine triphosphate) dependent chloride channel, found on the surface of epithelial cells of most exocrine glands. On opening, it allows chloride and bicarbonate anions to pass out of the cells (13). The movement of these anions maintains the electrochemical balance and hydration of various epithelial surfaces in the body, such as the lungs, pancreas, liver, gastrointestinal tract, reproductive tract and skin (14).

2.5.2 Mutations in CFTR

There are currently over 2000 mutations discovered in the CFTR gene (1), which have been divided into five classes, according to how they affect CFTR function (15). These are described below:

1. Class I mutations disturb protein synthesis caused by a premature Stop codon, due to nonsense mutations, frame-shift mutations and deletions. This results in an unstable protein that is easily degraded, leading to no expression of the CFTR protein. Examples include G542X, W1282X and R553X.

2. Class II, the most common form of mutation, disrupts protein maturation so that it cannot be correctly folded and processed in the endoplasmic reticulum before it is taken to the cell surface. These defects are caused by missense mutations and deletions. The most common mutation, Phe508del, falls into this class. It accounts for almost two thirds of mutations in CF. It is a deletion of three nucleotides, coding for phenylalanine, at position 508 in the amino acid sequence (16). Other examples of class II mutations include N1303K and I507del.
3. Class III mutations affect the nucleotide binding domains and are mostly missense mutations that alter the chloride channel itself, interrupting channel regulation and function. They result in reduced or no channel opening. Examples include G551D, G551S and G1349D.
4. Class IV mutations are usually missense mutations that affect the structure chloride channel pore, hence reducing the anion conductance. Examples include R117H, R334W and R347P.
5. Class V mutations are also missense mutations caused by a defect in the pre-MRNA splicing of the nascent protein. Consequently, there will be reduced synthesis of the protein, providing less CFTR protein at the cell surface. Examples include 2789+5G>A and A455E.
6. There is also a sixth class of CFTR mutation, which increases the turnover of the CFTR protein at the cell surface, reducing its stability (14,17). However this mutation has not been as thoroughly investigated as the other five defects (18) and therefore it is often grouped with the Class V mutations, as both result in a reduced quantity of protein (17).

2.5.3 Clinical consequences of CFTR mutations

In addition to assigning the mutations to the effect they have on a cellular level, CF mutations can also be categorised according to their clinical consequences. Historically, the two categories were “classic” CF and “non-classic” CF, with “classic” CF describing those patients with multi-organ disease. However, this distinction is not very useful in practice, which is why it is no longer used (18). Children within one family with the same genotype can present with different clinical features. There are areas in CF where the genotype-phenotype relationship is strong, such as in pancreatic sufficiency status. However, for characteristics such as pulmonary function, or whether a patient will develop diabetes, genotype does not usually predict phenotype.

There are many factors (other than the type of CFTR mutation) contributing to the health of CF patients, including lifestyle, environment, modifier genes, treatment and age. However, at present, we have limited knowledge of how these elements interact (19).

It is also important to note that not all CFTR mutations actually cause CF. These can be referred to as “polymorphisms” or “neutral variants” (20).

2.6 Pathophysiology

At the pathophysiological centre of CF is the defective ion transport across epithelial cells. This affects multiple body organs including the lungs, sweat glands, pancreas, liver, gastrointestinal tract and reproductive organs.

2.6.1 Respiratory System

An individual with CF does not have lung disease at birth. It is throughout childhood that the lungs become infected, first intermittently and then chronically (21, 22). The sections below explain some of the pathophysiology and hypotheses behind lung disease in CF.

a) Existing hypotheses

The pathophysiology of CF lung disease is very complex and not fully understood. CF produces a cycle of inflammation and infection leading to lasting airway damage, but there is still debate as to how this occurs (23) and whether inflammation or infection comes first. Poor bacterial elimination is thought to play an important role in the inflammatory response in CF lungs and there have been 3 main hypotheses that have been put forward to explain why this occurs: the "high salt", "low volume" and "pH" hypotheses. The "high salt" hypothesis proposes that a high salt concentration at the cell surface inhibits the activity of an important antimicrobial protein (human beta defensin-1) which normally acts as a defence mechanism against bacteria. Without this protein, the epithelial cells are more vulnerable to infection (24,25). However, other studies have found that, in both normal and CF patients, the airway surface liquid (ASL) is actually isotonic, rather than hypertonic (26).

The second theory, the "low volume" hypothesis, suggests that the defective chloride channels prevents an osmotic gradient occurring, so there will be very little water moving out of the epithelial cells. As such, the epithelial surface becomes dehydrated and the airway surface liquid (ASL) will be viscous and sticky. This results in an ineffective mucociliary clearance and hence higher susceptibility to infection (24). In vitro studies have shown that the ASL volume in CF epithelia is much lower than normal epithelia;

mouse models and human subject studies have also supported this hypothesis in the past decade. (27, 28, 24).

However, despite murine models supporting the “low volume” hypothesis, it is generally accepted that CF mice do not acquire spontaneous and chronic bacterial infections as seen in CF patients; therefore this animal model is unable to fully demonstrate respiratory pathology in CF (29).

The “pH” hypothesis proposes that as the faulty CFTR cannot transport chloride ions and bicarbonate ions sufficiently, the ASL is relatively acidic. This acidity diminishes antimicrobial activity in the ASL, impairing the killing of bacteria (30).

This hypothesis gained support after a 2010 study in which pigs were generated to have CFTR mutations; the pigs had a reduced ASL pH. The CF pig model revealed a great deal about the course of CF lung disease. At birth, the pigs’ lungs did not show signs of inflammation, much like humans with CF. However, after an intrapulmonary bacterial challenge, the CF pigs could not eliminate the pathogens as the healthy pigs could. This signified that the pig model also supported the theory that it is poor bacterial elimination which triggers the inflammatory cascade in CF, and hence the mucus accumulation and airway remodelling in CF lungs (23).

b) Inflammatory processes in the airways

When the inflammatory response occurs, there is a high production of inflammatory mediators such as interleukin-8 (IL-8). IL-8 attracts vast numbers of neutrophils to the lungs, which produce enzymes such as oxidases and proteases. The neutrophils are thought to be the main cause of pathology in CF lung disease, but the loss of immune-

regulatory mediators such as IL-10 are also thought to play a part (31). Chronically, this cycle of infection and inflammation causes lasting damage to the structure of the airways. The broncho-alveolar lavage (BAL) results from CF pig models showed changes consistent with chronic inflammation; these include airway remodelling with wall thickening and infiltration, goblet cell hyperplasia and mucus accumulation (23).

The CF pig model has therefore proposed that the introduction of infection leads to inflammation, but there is some indirect evidence that there may be an innate inflammatory process before the first bacterial infection occurs. One study found high numbers of macrophages (which are responsible for attracting neutrophils) in CF foetus lungs (32) and another study found increased numbers of neutrophils in the lungs of seven CF infants who had no infections at the time of BAL (33).

These conflicting theories demonstrate how complex the pathophysiology of CF really is and show that the inflammation/infection debate is far from settled. The CF pig model has provided some valuable insight into the pathogenesis of CF and has shown the consequences of spontaneous and chronic infections in CF lung disease. But of course, there are limitations to animal models. We cannot replicate CF in other animals just as the disease would present in humans. Furthermore, these models cannot fully incorporate phenotypic and environmental variation that occurs in human subjects.

2.6.2 Pancreas

Depending on their genotype, individuals with CF may develop pancreatic insufficiency. In fact, 85% patients will develop exocrine pancreatic insufficiency between the ages of 1 - 2 years (34).

The mutated CFTR gives rise to impaired bicarbonate and chloride transport into the pancreatic ducts, leading to a smaller volume of a more acidic fluid, causing precipitation of the secreted enzymes. This results in obstruction of the ducts and pancreatic damage (35). Indeed, pancreatic disease was also demonstrated in the CF pig model, where a fatty pancreas was found, as well as distended pancreatic ducts and fibrosis (23). Pancreatic insufficiency leads to poor digestion and subsequent malabsorption of fat, protein and fat-soluble vitamins, resulting in malnutrition (36).

2.7 Diagnosis

The sweat test is the most commonly used diagnostic test; newborn genetic screening is also available in many countries. In addition, there is an investigation available for determining pancreatic sufficiency status once the patient has been diagnosed with CF. Details of these tests (the sweat test, newborn screening and faecal elastase) are described below:

2.7.1 Sweat Test

The gold-standard diagnostic test for CF is the sweat test, in which the chloride concentration of the gland is measured. Pilocarpine is deposited onto the skin by iontophoresis in order to stimulate sweat gland secretion. Then, the sweat is collected with gauze or filter paper and analysed (37).

The sweat test should be performed after a positive newborn screening result when the infant is at least 2 weeks of age and weighs at least 2kg (38). However, if the newborn is

symptomatic, the test can be performed 48 hours after birth – if enough sweat can be collected. This can often be difficult, as the minimum volume of sweat required for a valid result should exceed 1 g/m^2 per minute (39).

If the test reveals sweat chloride values of ≥60mmol/L, it is considered abnormal and indicative of CF. Values between 40 and 59mmol/L are intermediate and values below 39mmol/L are considered normal. However, in infants under 6 months of age, the values are slightly different. Results ≥60mmol/l are still considered abnormal, but the intermediate range is 30-59 mmol/l and ≤29mmol/l means CF is unlikely (37).

As with most diagnostic tests, there are some pitfalls when relying on the sweat test result. Many CF patients have elevated sweat chloride concentrations, but some mutations, e.g. R711H, are associated with borderline or even normal test results (40). A CF diagnosis may take several years in these patients, during which time the child can develop chest symptoms consistent with CF.

Furthermore, the practicalities of performing a sweat test can be demanding, so user error and false results can occur. False positives may also occur in rare conditions such as Addison's disease, glycogen storage disorders and untreated hypothyroidism; however, these should be easy to differentiate clinically from CF (3).

2.7.2 Newborn Screening

Before a diagnostic test is used, all newborns in the UK are screened using the Guthrie heel prick, or blood spot test, in which a raised immune-reactive trypsinogen (IRT) is considered to be abnormal. The screening has been available for all newborns in the UK since 2007 (41). Newborn screening has some key advantages. Firstly, it will lead to a

prompt diagnosis, which means that the disease can be managed early on with the appropriate medication. This can prevent the child from developing early bronchiectasis, gastrointestinal problems (as a result of no PERT) and nutritional deficiencies, which may harm their growth and development. Secondly, newborn screening is said to encourage a proactive and preventative approach to the management of CF (42); indeed, recent evidence shows that early treatment of respiratory infection may improve the prognosis of CF patients (43).

Disadvantages of newborn screening include false-positive results or inconclusive results; both of these can cause undue stress and anxiety for families. This is especially true when the screening test produces a positive result, but the sweat test result is either borderline or normal (in the presence of 2 mutations, one if which is unclear). This is called “CF screen- positive, inconclusive diagnosis” or “CFSPID”. Infants with this diagnosis are often asymptomatic but can develop mild CF-related symptoms as they grow up. “CFSPID” is given as a diagnostic label to provide an explanation for families regarding their child’s condition and to activate appropriate support in healthcare settings (44).

After a raised IRT, further screening in the form of DNA testing can be carried out to determine the genotype of the individual. DNA testing can also be used for individuals with an intermediate chloride value to help ascertain the diagnosis (37). Once a diagnosis has been made, the individual’s relatives may be offered screening; the siblings are always screened to check for CF that has not been picked up and other adult family members can be screened to check for carrier status (11).

2.7.3 Faecal Elastase

To determine pancreatic sufficiency status, the faecal elastase-1 enzyme is measured in the individual's stool. This test is non-invasive and easy to perform, as well as being more sensitive and specific than direct pancreatic stimulation tests (45). This is because there is significant correlation between faecal and duodenal elastase-1 concentration and the concentration of duodenal lipase, amylase, trypsin and bicarbonate (46).

2.8 System Involvement and its management

In this section I will discuss the clinical consequences and management of the systems most affected in CF: the respiratory system, the endocrine system, the gastrointestinal and hepato-biliary system and the reproductive system.

2.8.1 Overview

There is a definite multi-disciplinary approach in the management of CF. The team is comprised of doctors, pharmacists, physiotherapists, dieticians, psychologists, social workers, nurses and research coordinators. Such a large team is required because CF is a multi-system and multifactorial condition, incorporating both the individual and their family members. Patients become rather accustomed to the clinical setting. They attend frequent appointments (usually every 2-3 months) where they meet with members of the CF team to track their progress. Not only do they need medication, but they also require dietary input, airway clearance techniques and psychological and/or social support.

Individuals are also closely monitored with investigations, either at each appointment, yearly, or when they become unwell.

2.8.2 Respiratory System involvement

The respiratory tract is the most affected system in CF and respiratory failure will most likely be the cause of death (11). The clinical presentation of CF varies according to age and genotype and, as mentioned above, individuals are not born with lung disease: lung disease usually develops during early childhood.

Infants develop recurrent respiratory symptoms such as a cough, wheeze, dyspnoea, episodes of bronchiolitis and pneumonias. Nose polyps and sinusitis may also occur (11). The cough itself may initially present as a recurrent, dry one that will usually go on to produce mucus and, eventually, purulent sputum (47). As the disease progresses, the build up of thick, viscid mucus in the lungs leads to recurrent chest infections involving specific bacteria and the individual can become chronically infected. The most common bacteria are *Staphylococcus aureus, Haemophilus influenzae* and, ultimately, *Pseudomonas aeruginosa* and *Burkholderia* species. Chronic infections with these bacteria may cause bronchial wall damage, bronchiectasis and abscess formation (16). *P. aeruginosa* is often found in adults with CF as it can be difficult to eradicate once the bacteria is deep within the lung tissue. A complication that can occur with *B. Cepacia* is "Cepacia syndrome", which is a combination of bacteraemia and necrotising pneumonia. It produces bilateral nodular consolidation and cavitation and can result in respiratory failure (48).

In well-established disease, there are certain signs to observe during examination. Finger clubbing may suggest advanced lung disease (although it not an accurate marker of disease severity) and the lungs can be hyper-inflated (as a result of air trapping) with coarse, inspiratory crepitations and an expiratory wheeze (16).

Other complications of CF include pneumothorax, lobar collapse, pulmonary hypertension, (due to chronic hypoxia) Aspergillus- related lung disease and haemoptysis. Pneumothorax arises from mucous plugging in the airways, which leads to a relatively high alveolar pressure. If this pressure exceeds the interstitial pressure, air can leak out of the alveoli into the pleural space, causing a pneumothorax. Mucous plugging also has a role to play in lobar collapse (48).

The complications described above- accompanied by thick secretions immersed in chronic bacterial infection, airway inflammation and associated oedema (and eventual respiratory muscle weakness)- may all contribute to respiratory failure (49).

2.8.3 Management of the Respiratory System

a) Monitoring

Patients are separated according to their bacterial-colonisation; for example, Pseudomonas-infected patients are grouped together in one clinic to prevent the infection of non-colonised patients. At every appointment, the clinician should conduct a history and respiratory examination to determine the patient's respiratory signs and symptoms (or lack thereof). The physiotherapist should also assess the quality of the patient's airway clearance techniques (see below) and ensure that they have a regular physiotherapy routine.

Pulmonary function tests are conducted every appointment to monitor the FEV1%. The patient's oxyhaemoglobin saturation is also noted and a sputum sample is taken (47). On a yearly basis or when the patient develops respiratory symptoms, a chest x-ray is

performed. Clinicians may also request a CT-scan of the chest to look for subtle changes in the lungs that may not be easily identified on a plain radiograph.

a) Physiotherapy

Airway clearance is a key component of CF management, so various physical therapies are utilised in the treatment of CF. These are comprised of the different airway clearance regimens and physical training. Examples of airway clearance techniques include Conventional Chest Physiotherapy (CCPT), Positive Expiratory Pressure (PEP), Active Cycle of Breathing Techniques (ACBT), Autogenic Drainage (AD), mechanical percussion and High-Frequency Chest Compression (HFCC). The general consensus among healthcare professionals is that airway clearance techniques encourage muco-ciliary clearance by altering airflow and mucous viscosity. Furthermore, short -term trials demonstrated the benefit of airway clearance techniques compared no airway clearance techniques. However, the comparative efficacy of individual airway clearance techniques seems to be a subject needing further research, as there is limited evidence on this at present.

Individuals with CF are also encouraged to maintain an active lifestyle; there is some evidence to suggest that physical training is a useful addition to the CF care-plan (50).

b) Antibiotics

Antibiotics are a large part of CF management. They are given prophylactically and also for infective exacerbations. Individuals with CF are more susceptible to infection with organisms such as *P. Aeruginosa, Aspergillus, B. Cepacia and Methicillin-resistant Staphylococcus aureus* (MRSA). If chronically infected, these organisms can have a

detrimental effect on the patient's lung function. Infected patients should therefore receive a prompt eradication regimen.

Treatment regimens will vary according to the CF care centre, but for mild infections an oral antibiotic is usually given. If the infection becomes more severe, the exacerbation is treated with intravenous antibiotics. The choice of antibiotic is dependent on the organism cultured, its sensitivities, the patient's previous clinical response to certain antibiotics and previous allergic reactions.

Oral corticosteroids are sometimes given with a course of antibiotics to treat an infective exacerbation, but are not recommended for chronic use unless the patient has asthma or allergic bronchopulmonary aspergillosis (ABPA) (51).

In terms of prophylaxis, all patients who are chronically infected with *P. aeruginosa* should be given long-term, nebulised anti-pseudomonal therapy. Furthermore, for infants under two years of age, anti-staphylococcal oral antibiotics should be given for prophylaxis (51).

c) Anti-inflammatory agents

Based on a 2016 Cochrane review, there is evidence to suggest that the use of ibuprofen twice daily can slow the progression of mild to moderate lung disease in CF. However, clinicians should be aware of its adverse effects on renal function, especially if used alongside potentially nephrotoxic drugs, such as aminoglycosides (52).

d) Mucolytics

One of the main features of CF is an excess of thick, sticky mucus produced by the lungs and medications are required to shift these secretions. The most commonly used

mucolytics are Human recombinant DNase (Dornase alfa) and Hypertonic saline, both administered via a nebuliser. Dornase alfa works by degrading the DNA within CF mucus, thereby decreasing its viscosity. Hypertonic Saline works by osmosis, drawing fluid into the lumen of the airway, increasing the hydration of the airway surface liquid (53). In a controlled trial, hypertonic saline was shown to decrease the overall number of exacerbations and antibiotic use for exacerbations; although there was no significant effect on the rate of change in lung function, hypertonic saline was associated with a moderate, sustained improvement in the level of lung function (54).

Chronic use of Dornase alfa and Hypertonic Saline are therefore recommended for CF patients who are 6 years and older to improve lung function and reduce exacerbations (51).

Other mucolytics are N-acetylcysteine (NAC) and mannitol. N-acetylcysteine works by breaking disulphide bonds in mucus, which decreases its viscosity. However, the CF foundation does not recommend NAC for chronic use, due to lack of sufficient evidence on the subject. On the other hand, inhaled, dry powder (mannitol) has been shown to improve lung function after prolonged periods of use (51). NICE has recommended mannitol for patients who are not suited to dornase alfa and other osmotic agents, and whose lung function is rapidly worsening (55).

e) Lung Transplant

Lung transplantation is reserved for end-stage CF for those patients who are not responding to medical therapy, to the extent where the individual is hypercapnic and/or needing supplemental oxygen. As with all transplants, there are some contraindications to lung transplantation. Sepsis, multi-organ dysfunction and colonisation with

Burkholderia Cepacia are among the absolute contraindications, but other factors are assessed For example, the patient's nutritional status, how well their diabetes is controlled and overall functional ability (56). Post-lung transplant survival is improving all the time, with figures at around 68% survival at 5 years, compared to 33% at 5 years for no transplantation (57).

2.8.4 Endocrine System involvement

Due to the destruction of pancreatic tissue in CF, many patients will go on to develop CF-related diabetes mellitus (CFRD). The incidence is four times more common in those aged 16 and over, compared to those between the ages of 10 and 16 (8). This is due to the progressive nature of the destruction of pancreatic tissue from exocrine pancreatic insufficiency. Over time, fibrosis and fatty infiltration destroys beta islet cell structure. There is also evidence from mouse models that CFTR dysfunction itself may also contribute to pancreatic inflammation. The pancreatic tissue of CF mice revealed focal inflammatory cell infiltrates without specific injury to the pancreas, suggesting that there is a certain amount of intrinsic pancreatic disease in CF (58).

These changes to the pancreas in CF result in poor beta cell function and therefore a lack of insulin. As well as a lack of insulin, resistance to insulin (such as in type II diabetes) may also have an important part to play in the pathophysiology of CFRD. Insulin resistance in CFRD is thought to be due to factors such as anti-inflammatory therapy, (i.e. corticosteroid use and increased oxidative stress) which may lead to impaired translocation of important glucose transporters at the cell surface (59, 58).

CFRD often presents insidiously; not all patients will experience the classic symptoms of hyperglycaemia (fatigue, polydipsia and polyuria) (58). Clinicians may suspect it in CF

patients who are excessively tired and fail to gain weight, despite a good diet and correct Creon® dosage.

2.8.5 Management of the Endocrine System

Patients with pancreatic insufficiency are more likely to develop CFRD, so the CF team take measures to screen, monitor and manage patients who are at risk.

The oral glucose tolerance test (OGTT) is the standard investigation for screening CFRD, but other, perhaps more sensitive tests can be used to detect pre-diabetic patients. These tests include continuous glucose monitors, glucose or insulin area under the curve (AUC) or mid-OGTT assessment of glucose level (60).

CFRD is treated with insulin. The regimen is decided upon by the clinician, based on what they believe will most suit the patient. Mostly, patients are treated with a basal-bolus regimen (61). A team of professionals specialising in diabetes guide the management of CFRD. Patients attend a specialist CF diabetic clinic in which endocrinologists and diabetic nurses review their glucose control and can adjust the dose of insulin if required.

2.8.6 Gastrointestinal and Hepato-biliary System involvement (excluding constipation and DIOS)

7-10% neonates will present with meconium ileus, in which the meconium obstructs the intestine and signs of bowel obstruction are observed, such as bilious vomiting and abdominal distension. If untreated, it can lead to perforation and peritonitis. Neonates with CF are also more likely to present with surgical abdomen pathologies, for example,

volvulus and gut atresia. Infants and young children may also present with rectal prolapse (47).

Over 90% of individuals with CF have pancreatic exocrine insufficiency, in which the enzymes (lipase, amylase and proteases) are defective. Pancreatic ducts become blocked with the thick, viscid mucous, leading to poor digestion of fats, proteins and fat- soluble vitamins (A,D,E and K): this can lead to malabsorption (16); the malabsorption results in steatorrhoea (malodorous, greasy stools, difficult to flush), increased frequency of stools, abdominal pain, distension and nutritional deficiencies.

Individuals can also present with acute pancreatitis. Viscid mucous in the pancreas can cause the ducts to become obstructed, increasing the pancreatic ductal pressure and triggering the unregulated activation of trypsin within acinar cells (62).

Liver and biliary tract problems can also be a complication for individuals with CF. They are much less common than pulmonary and pancreatic disease, affecting about a third of patients in the first decade of life (63). Neonates may uncommonly present with obstructive jaundice (11) and older children can develop cirrhosis (with or without portal hypertension) and gallbladder disease (8).

1.8.7 Gastrointestinal and Hepato-biliary system management

a) Nutritional Interventions

The dietician guides the management of nutritional interventions in CF. At each clinic appointment, the patient's height, weight and BMI are measured and the dietician reviews the patient's diet. On occasion, they may ask the patient to fill out a food diary to

ascertain if there is a calorie or nutritional deficit. From this, the dietician can advise the patient (or parents of the patient) on foods to incorporate into the diet. Annually, patients have a blood test to measure their vitamin A, D and E levels and a coagulation profile to measure their vitamin K levels. Due to pancreatic insufficiency, most patients with CF do not effectively absorb fat-soluble vitamins A, D, E and K. Therefore, these vitamins must be given regularly based on the patient's blood vitamin levels (prothrombin time is used to measure levels of vitamin K) and based on CF nutritional recommendations (64).

Pancreatic insufficient patients also require Pancreatic Enzyme Replacement Therapy (PERT). These are given as oral capsules called Creon®, made up of lipase, amylase and protease, which should be taken with every food intake. In babies, enzyme granules called Creon Micro® are used instead. These are usually given before feeds with a small spoonful of fruit puree. The fruit puree prevents the granules from degrading in the gastric acid, but also makes it easier for the infant to swallow (64).

The CF dietician decides on the dose of PERT, based on the patient's clinical symptoms (e.g. degree of steatorrhoea) and fat content of the diet. Proton pump inhibitors, such as omeprazole, can be given to further aid the action of PERT.

Patients with CF have much greater energy demands than healthy individuals (65) and, unfortunately, it can be difficult to always meet those demands. In addition to meals, high-energy supplements are given to those individuals failing to thrive, or whose appetite may be declining. If oral supplements are not sufficient, patients may need tube feeding to complement their oral intake. This can either be in the form of an over-night

nasogastric tube or a gastrostomy tube. For long-term use, a gastrostomy tube is preferred, as the process of feeding is usually more comfortable for the patient (64).

b) Liver and biliary tract problems

As well as examining patients for signs of liver disease (such as an enlarged liver) at each clinic visit, clinicians should request additional tests as part of a patient's annual review. These tests usually include an abdominal ultrasound scan to visualise the liver and biliary tree and liver function tests for measuring levels of serum liver enzymes.

For established hepato-biliary pathology, Ursodeoxycholic acid is recommended. It works by displacing toxic bile acids from the circulation and is also thought to have a protective effect on cell membranes that are exposed to bile acids (66).

Constipation, incomplete DIOS and complete DIOS are fully described in section 2.14, as these are the mainstays of my thesis.

2.8.8 Reproductive system involvement

Although females are not technically infertile from CF, the cervical mucus is often too viscid to allow the passage of sperm through the cervical canal. Poor nutrition in CF may also reduce fertility, as amenorrhoea is more common in women with a lower percentage of body fat (67).

Males are generally more affected than females, with over 98% infertile as a result of the congenital, bilateral absence of the vas deferens with azoospermia (CBAVD). The azoospermia is also relatively acidic, due to the defective bicarbonate ion transport. The bicarbonate transport is essential for readying the sperm for fertilisation, an event called

capacitation. This, therefore, leads to an impaired fertilising capacity of the sperm (68). Other pathologies include absence or atrophy of the epididymis and seminal vesicles (69).

2.8.9 Bone involvement

CF patients are more likely to suffer from osteoporosis than healthy individuals, with one third of adults affected. As such, they will have regular dual-energy X-ray absorptiometry (DEXA) scans to monitor their bone density. Patients are already recommended to take vitamin D, but may also be given calcium and bisphosphonates if the clinician deems it necessary (70).

2.9 Psychological problems associated with CF

Psychological input from the multi-disciplinary team is an important factor in the management of CF because many individuals struggle (in different ways) in growing up with a chronic disease. The next sections will describe some of the psychological implications of having CF throughout childhood, adolescence and adulthood.

2.9.1 Childhood

During early childhood, medical procedures and treatments can cause stress for children who do not fully understand their necessity. The child may perceive these procedures as painful, uncomfortable or intimidating, resulting in an intense behavioural reaction. They then associate future similar experiences with heightened emotion and distress, thus approaching further encounters with greater resistance.

A limited understanding of their condition also means that many young children do not appreciate the importance of taking their regular medication, following their physiotherapy routine or eating a high calorie meal. This can be stressful for families and negatively impact parents' mental health and family dynamic. In fact, parents who have a CF child are two to three times more likely to suffer from depression, anxiety - or both- compared to the general population (71, 72).

Furthermore, sibling relationships may become problematic in families with a CF child. Due to the large amount of time that must be dedicated to activities such as physiotherapy, appointments and medication administration, the healthy sibling may feel as though the CF child is getting more attention from the parents (72).

2.9.2 Adolescence

At school age and adolescence, children desperately want to be accepted by their peers, yet individuals with CF may feel as though they do not fit in. Various factors can account for this, whether those are specific CF behaviours such as excessive sputum production, taking Creon® in front of friends, or feeling singled out by teachers.

It can be especially difficult for adolescents whose symptoms are often worsening just as the point when they feel most insecure. Adolescents may also begin to wonder about what their future holds and the growing complexity of peer relationships and discovering their sexuality adds to these feelings of angst and confusion (72).

Then there are issues surrounding body image. In an era where social media plays such a prominent role, teenagers of today probably place more importance on their appearance than ever before. The fact that a high calorie, high fat diet is emphasised in CF may be

conflicting for some adolescents who hear otherwise from peers or online. Not to mention the fact that their weight is monitored very closely with measurements at every appointment. Although the prevalence of eating disorders is no different to the general population, it is not surprising that there is a greater degree of eating disturbance and negative eating attitudes in CF: 53% compared to 40-47% in their counterparts (73, 72).

2.9.3 Mental health in CF

With regards to mental health issues, anxiety seems to be the condition most prevalent in adolescents with CF (74). Some studies claim that symptoms of both depression and anxiety are elevated in patients compared to the general population (71), but others find that depression does not significantly affect patients with CF (72).

For adult patients, increasing age, unemployment due to their CF and worsening pulmonary function seem to be connected to mental health issues (75).

2.10 Prognosis

Currently, the median life expectancy for someone with CF is 41 years old, although a baby born today could be projected to have a median life expectancy of 56 years if the mortality rate continues to decrease at the rate observed between 2000 and 2010 (76).

The next sections will explain the different factors that may affect prognosis, such as the patient's genotype, pulmonary function, nutritional status, treatment adherence and pancreatic sufficiency status.

2.10.1 Effects of genotype on prognosis

A 2003 study found a significant difference in standardised mortality between mutation class II (higher mortality) and classes IV and V, with class IV possessing the lowest mortality rate. Researchers also found that patients with the most common class II mutation- Phe508del- presented with pancreatic insufficiency and had worse nutritional outcomes than other mutations.

However, this same study acknowledged that there appear to be significant differences in phenotype and mortality between several Phe508del heterozygous genotypes, as well as differences within the same class (77). These findings are similar to the differences in phenotype and class studied by Boeck (19). The non-Phe508del allele in heterozygotes can also play a part in the relationship between mortality and phenotype; as mentioned in section 2.5.3, there may be non-CFTR genes that alter the disease progression and could potentially protect against certain aspects of CF (77).

2.10.2 Effects of gender on prognosis

Although the relationship between genotype and phenotype is complex and sometimes difficult to ascertain, there are many other aspects of the disease that can also affect prognosis. A study on “The Gender Gap in Cystic Fibrosis Mortality” in 1997 found poorer survival in females compared to males between the ages of 1-20 years (78). Even in 2014, an observational death registration study found that the median age at death for males was greater than females, showing that this gender gap has not narrowed since 1997 (79).

This is most likely multifactorial in aetiology, as stated in both papers. One logical reason could be that women are more likely to be underweight than their male counterparts and poor nutrition is associated with poor outcome (see CF complications below).

Some theories claim that the female sex hormone, 17-beta- estradiol, further dehydrates the airway surface liquid and can heighten the Toll-Like Receptor responsiveness to a range of bacteria (80).

2.10.3 Effects of CF complications on prognosis

Morbidities associated with CF can have an impact on the overall prognosis, for example respiratory microbiology and chronic infection, pancreatic insufficiency, CF related diabetes (CFRD) and CF related liver disease.

Chronic infection with organisms such as *P.Aeruginosa, S. Aureus* and B. *Cepacia* complex has the biggest influence on Forced Expiratory Volume in 1 second (%FEV1) in CF (80).

%FEV1 is one of the most reliable indicators of pulmonary function and hence prognosis in CF (81). A 1992 study established that patients with a %FEV1 < 30% had a 2 year mortality over 50% (82). Although this finding is not fully reliable according to more recent studies (81), it still illustrates the significance of pulmonary function in CF prognosis.

Pancreatic insufficiency is also associated with significant decreases in FEV1% and patients with pancreatic insufficiency are twice as likely to develop severe lung disease (%FEV1<40% predicted) (80, 83). Pancreatic insufficiency is also related to fat

malabsorption and therefore poor nutrition, which is a risk factor for poor outcome in itself.

Another predicator or poor outcome is CFRD, which is associated with insufficient nutritional outcomes and more severe lung disease - both predictors of poor prognosis (80). Liver disease is also a serious morbidity of CF as it is the third highest cause of death after respiratory failure and transplant complications (83).

Overall nutritional status of the individual affects prognosis, as demonstrated in a 2006 study looking at risk factors for death amongst CF patients awaiting lung transplantation. They found that those requiring nutritional intervention had a higher risk of death compared to their counterparts (84).

CF complications are related to one another and it is important to appreciate that one complication may lead to or worsen others. For example, respiratory complications, CFRD, gastrointestinal and hepato-biliary complications all affect the nutritional status of the patient. If the patient's nutritional status is poor, they will be less mobile, have lower energy levels and mood, which may affect their adherence to treatment. The cycle of poor health therefore continues and so it is essential that we appreciate the inter-dependence of these factors.

2.12 The Future of CF

In the previous section I discussed the current MDT management of CF. There has also been a great deal of research looking into new treatments for the disease, which I will discuss in the following sections.

2.12.1 Genotype-specific small-molecule therapy

In recent years there have been great advances in the field of CF, namely research around small molecule therapies. One of the most successful of these is the drug, Ivacaftor. Unlike other CF medications, Ivacaftor works by targeting CFTR itself, potentiating the action of channel opening so that chloride ions can pass through. Ivacaftor has proven to be very effective at targeting the G551D mutation. In a phase III, randomized, double-blind, placebo-controlled trial over a 48- week period, the drug maintained a significant treatment effect at a %FEV1 that was 10.5 percentage points greater than the placebo. Furthermore, after adding the patients' usual treatments to Ivacaftor, (dornase alfa, oral azithromycin and inhaled tobramycin) the change in %FEV1 was even greater, at 17.2% improvement compared to the placebo. This was also sustained for 48 weeks. At week 48, 67% patients in the Ivacaftor group (compared to 41% in the placebo) were also free from pulmonary exacerbations (85). This treatment is currently licensed for all patients (2 years and above) with the G551D mutation (10). Unfortunately, Ivacaftor is a very expensive treatment. In the UK, the cost stands at £182,000 per patient per year. This had led to more rigid testing of the clinical benefit of Ivacaftor, which may limit its use for other mutations (86).

Ivacaftor was also tested for the most common mutation, homozygous Phe508del, but was shown to have very limited efficacy (86). The overall adverse effect frequency was similar to the placebo group (87.5% in the ivacaftor group and 89.3% in the placebo group) and the overall difference in the change in FEV1% between the two groups was just 1.7% (87).

Following on from the research on Ivacaftor, another small molecule therapy was produced: Lumacaftor. Lumacaftor was originally created for the homozygous Phe508del mutation but was shown to be unsuccessful in phase II clinical trials. However, the combination of both Ivacaftor and Lumacaftor brought success to both phase II trials and phase III trials with significant improvements to the %FEV1 (86). It was therefore licensed for use in 2015 (88). Unfortunately, due to the exceptionally high cost of this drug, NICE does not currently recommend it for CF. Although the improvement in %FEV1 was significant, it was relatively modest, ranging from 4.3 to 6.7% compared to the placebo. This moderate improvement at such a high cost is perhaps why NICE has not approved the combination of Lumacaftor and Ivacaftor for the Phe508del mutation (89).

2.12.2 Gene therapy

An ongoing area of research in CF is in gene replacement or editing therapies to correct CF mutations before the disease manifests itself. The UK CF gene consortium published results of a randomized, double blinded, placebo-controlled phase IIb trial done in 2015, of which the results were encouraging, but not yet suitable for clinical care. It was encouraging that there was a small but statistically significant improvement in %FEV1 with the pGM169/GL67A gene therapy formulation. However, this was mainly driven by a fall in the %FEV1 in the placebo group (90). The same organisation is also planning to conduct a clinical trial in 2017 using a Lentiviral vector gene therapy. So far, they have not experienced any problems in the preliminary safety studies and the data supports the progression of the vector into a first-in-man CF trial in 2017.

2.14 Distal Intestinal Obstruction Syndrome

2.14.1 Overview

DIOS is a gastrointestinal complication of CF. It is distinct from constipation (another complication in CF) in its pathophysiology, although the two are often confused with one another in clinical practice. Constipation occurs when there is faecal accumulation throughout the colon (91). Individuals have infrequent bowel movements (<3 per week) and stools become hard and lumpy. Patients may also experience straining and feelings of incomplete evacuation and anorectal obstruction (92).

DIOS, however, occurs when thick, sticky mucus produced in the CF intestine combines with viscid faecal material in the lumen of the terminal ileum and/or caecum. The mass adheres to the intestinal crypts and villi, making it very difficult to pass per rectum (91). This can block the lumen either partially (incomplete DIOS) or fully (complete DIOS).

In this section, I will firstly review the literature for chronic constipation, as it is a common gastrointestinal complication in CF that is often confused with DIOS. I will then go on to outline the epidemiology, risk factors, aetiology, pathophysiology, diagnosis, clinical features and treatment of DIOS.

2.14.2 Constipation

a) Epidemiology

There are very few reports on the lifetime prevalence of constipation in patients with CF. The most recent annual data report (8) does not contain any information on constipation

in CF, but available figures show that it is a very common problem, occurring in 26-47% paediatric patients and 42% adult patients (93, 94).

b) Risk factors

The correlation between pancreatic insufficiency and constipation is generally acknowledged, but there are some conflicts in the literature (95).
However, 2010 study by Van der Doef demonstrated that patients with constipation had a lower mean total fat absorption to patients without constipation (86% in patients with constipation compared to 90% in patients without constipation) (96). Indeed, two other studies have shown that high doses of pancreatic enzyme supplements correlate with constipation (97, 98).

Although the constipation management guidelines recommend a high fibre diet and good hydration, (see below) research has found that there is no correlation between these lifestyle factors and CF constipation (96, 99).

There are many other risk factors for constipation, although it is important to note that these are not specific to CF. In children, toilet training issues and psychological issues may play a part in aggravating the issue; constipation is often painful and may lead to children suppressing defecation. The lower colon becomes distended and the urge to defecate becomes irregular due to a decrease in rectal sensation (100).

In both children and adults, physical inactivity is a risk factor for constipation. It is important to be aware of this especially during the later stages of CF when the patient's overall health has declined and their activity levels may be very low.

It is also important for clinicians to be aware of medications that may cause constipation; these include antidepressants, calcium supplements, iron supplements, antiepileptics and sedating antihistamines (101).

c) Diagnosis

The Rome III criteria are generally used to diagnose constipation. A patient must have experienced at least 2 of the following symptoms in the past 3 months: fewer than 3 bowel movements per week, straining, lumpy or hard stools, sensation of anorectal obstruction, sensation of incomplete defection and manual manoeuvring required to defecate (92).

Sometimes it can be difficult to differentiate between incomplete DIOS and severe constipation in clinical practice and they may both present with abdominal pain and a mass felt on abdominal examination. Unlike DIOS, constipation runs a more gradual course, whereas DIOS tends to present more acutely. Constipation is also more likely to present with a left-iliac fossa mass (rather than the right-iliac fossa mass in DIOS) as it is found in the colon.

To further clarify the differences between constipation, incomplete and complete DIOS in CF, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) CF working group has set out simple clinical criteria for each condition (102). This was done in a cohort of patients under 18 years of age across 8 CF centres between 2001 and 2005. The definitions for DIOS can be found later in this section.

The ESPGHAN group defined constipation as “gradual faecal impaction of the total colon”. Their criteria for constipation in CF is shown in Table 1.1:

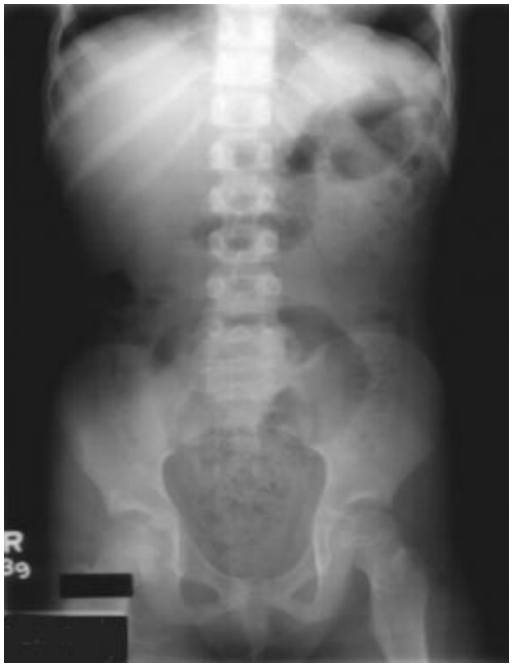
Table 1.1: Criteria for diagnosing constipation (102**)**

ESPGHAN CF Working Group definition for constipation in cystic fibrosis.
No. 1 Abdominal pain and/or distension
No. 2a Reduced frequency of bowel movements in the last few weeks or months
No. 2b Increased consistency of stools in the last few weeks or months
No. 3 Symptoms 1 and 2 are relieved by the use of laxatives
Constipation: no. 1 or no. 2a or no. 2b and no. 3

Radiology can also be used to aid diagnosis in constipation if there is doubt in the clinical picture. A plain abdominal radiograph is typically used, which shows faecal loading throughout the colon (91). However, it is worth noting that in clinical practice, constipation can usually be diagnosed with a detailed history, abdominal and rectal examination. X-rays expose the patient to radiation and should therefore not be used routinely.

The figure below shows a plain abdominal radiograph of a patient with constipation.

Figure 2.1: Plain radiograph of constipation



This figure shows a paediatric patient with stool throughout the colon (103).

d) Management of constipation

Before starting medical treatment, it is recommended that clinicians ensure their patients are adequately hydrated and on a balanced diet with good fibre intake. First-line treatment for constipation is commonly an osmotic laxative, such as polyethylene glycol 3350, under the brand name Movicol®; this should be given on an escalating dose regimen. Movicol® comes in sachets of oral powder and can be given in different strengths and forms, depending on the age of the patient and the indication. For chronic constipation, the national guidelines recommend 1 to 3 sachets daily in divided doses for up to 2 weeks and 1 to 2 sachets daily for a maintenance dose. For faecal impaction, the patient may be given up to 8 sachets on the first day, after which the dose is reduced. There is also Paediatric Movicol® which is administered at a dose of 1 sachet per day for children aged 2 to 5 years and 2 sachets per day for children aged 6 to 11 years. Another commonly used osmotic laxative is Lactulose. Lactulose is given as an oral solution; the

doses are 15ml twice per day for adults, 5 to 20ml twice per day for children aged 5 to 17 years and lower doses (2.5 to 10ml) for children aged 1 to 4 years. If the condition fails to resolve within 2 weeks, a stimulant laxative can also be added or substituted if the osmotic laxative is not tolerated; for example, senna, sodium picosulphate or sodium docusate (which also has stool softening properties). Senna is taken orally and can be given as a tablet or as syrup. Younger children are usually given syrup; the dose is 3.75 to 15mg once daily for patients aged between 1 and 3 years. This can be increased to 30mg (as a tablet or syrup) for older children aged up to 17 years. Adults can take a tablet or syrup at doses between 7.5 and 30mg once daily. Adults can take sodium picosulphate at a dose of 5 to 10mg once daily; children under the age of 17 can take it at a dose of 2.5 to 20mg once daily, which is adjusted according to the response. Sodium docusate can be given to patients aged over 12 years at a daily dose of up to 500mg. Children aged between 2 and 11 years can take between 12.5 and 25mg 3 times per day in the form of an oral solution. If the response to oral medication is not sufficient, a stimulant enema or suppository is recommended for adults (101, 104)

2.14.3 Historical background of DIOS

DIOS was previously known as Meconium Ileus Equivalent (MIE), first described in 1962 in the case of a 15 year- old boy. At the time, he was apparently treated with pancreatin via an ileostomy to relieve the obstruction (105). It is important to note that children with bowel obstruction had previously been described in CF in the 1950s, but they were not named “MIE”(4).

A very popular treatment of MIE in the 1960s and 70s was oral n-acetylcysteine (NAC), also used to treat meconium ileus in neonates. The first documented use of this in post-neonatal meconium ileus was in 1967 (106). Another drug used to successfully treat acute MIE, first described in a 1986 study, was diatrizoate maglumine (Gastrografin®) (107). Both NAC and diatrizoate are still used to treat DIOS in many centres today.

The use of pancreatic enzymes (e.g. pancreatin), mucolytics (e.g. NAC) and enemas were deemed unhelpful for the treatment of MIE in a 1986 Lancet article, just after MIE was given the name DIOS. The article described them as “neither predictably effective, nor rapid in action” (108). There are quite a few contradictions in historical literature on the subject of DIOS treatments. A proportion is made up of case studies. One should judge these studies with a critical eye, as they can be subjective and may only apply to one patient or a small group of patients, rather than the general condition.

2.14.4 Epidemiology of DIOS

DIOS affects 10% to 22% of individuals with CF (109, 110). One study found that children with CF had complete DIOS at a rate of 5 to 12 episodes per 1000 patients per year, with higher figures for incomplete DIOS (102). The CF annual report shows an increase in intestinal obstruction for adults with CF (7.4%) compared to those under the age of 16 (3%) (8). However, there appear to be disparities in the literature because in 2016 Munck found similar incidences of DIOS between children and adults (111). The reason for this difference is probably due to other factors that can increase likelihood of developing DIOS. For example, once an individual has had DIOS the recurrence risk can be as high as 77% (112). It also occurs in more individuals who have pancreatic enzyme deficiency and

is anecdotally more common in those who do not adhere to pancreatic enzyme replacement therapy (113). There are many risk factors to consider for DIOS, as illustrated in Table 1.1 (91).

Table 1.2 Risk factors for DIOS (91)

• Severe genotype
• Pancreatic insufficiency
• Dehydration
• Poorly controlled fat malabsorption
• History of meconium ileus
• History of DIOS
• Post organ transplantation
• CF related diabetes

2.14.5 Pathogenesis of DIOS

In the gastrointestinal tract there are various events likely to predispose an individual to bowel obstruction. This section will describe the various pathophysiological and cellular factors contributing to the development of DIOS.

a) The ENaC Theory

Principally, as with other organs in the body, the defective CFTR gives rise to low levels of chloride and water in the gut lumen. There is also an increase in the number of epithelial sodium channels (ENaC) in the CF gut, due to a fault in normal down-regulation of these channels by CFTR; more ENaC results in more sodium and fluid absorption from luminal mucus (114). These two phenomena create a dehydrated environment in the intestinal lumen, as well as thick, viscid mucus, predisposing the individual to faecal impaction (91). To scrutinise the ENac theory, one should consider that we are yet to fully comprehend

exactly how its regulators affect human physiology after seeing these promising results on animal and cellular models (114).

b) Bile acid physiology

There is also evidence of abnormalities in bile acid physiology in CF. Bile acids usually induce secretion via CFTR and are normally reabsorbed into the terminal ileum. In CF, these mechanisms are affected due to the faulty CFTR. The involvement of the terminal ileum in DIOS supports this theory (115).

c) Bicarbonate levels

In CF, there are also relatively low levels of bicarbonate in the duodenum. This leads to a rather acidic environment in the duodenum, as the gastric acid from the stomach cannot be correctly neutralized. This means that the pH of the duodenum will not be adequate for the digestive function of pancreatic enzymes and bile salts, contributing to the relatively poor digestive function of the small intestine in CF (116). Furthermore, the bicarbonate is said to help maintain the normal solubility of intestinal mucus, so it follows that there will be an accumulation of mucus if the bicarbonate levels are not suitable (117, 118).

d) Fat Malabsorption

Fat malabsorption as a result of pancreatic exocrine insufficiency has been associated with the development of more viscid faeces in the intestine, and hence the development of DIOS. However, this theory is controversial because DIOS can also occur in those who are pancreatic sufficient (119 ,91)

e) Inflammation

Inflammatory processes may also have a part to play in the pathogenesis of DIOS. Recent studies have shown that submucosal or transmural inflammation is common in patients with DIOS. This inflammation has been linked to enteric neuromuscular dysfunction, which may be one of the mechanisms behind faecal impaction (120).

The muscularis mucosa is often thickened in patients with DIOS too, which may be as a result of dysmotility, or due to the dense and sticky intestinal contents (121).

In summary, there are various mechanisms involved in the pathogenesis of DIOS, some more well recognised than others, as this section as highlighted. Currently, the overall significance of each mechanism in the full picture of DIOS is not completely clear, but one can deduce that the faulty CFTR is most likely at the core of the whole process, especially since those with a severe genotype are most likely to develop DIOS. However, there are clearly more complex factors at play because DIOS is also seen (albeit rarely) in those with mild genotypes (111).

2.14.6 Clinical features of DIOS

Individuals with complete DIOS present with signs and symptoms of bowel obstruction: abdominal pain, distension and vomiting (122). If the individual presents more intermittently - with episodes of abdominal pain, nausea or anorexia without vomiting - the diagnosis is more likely to be incomplete DIOS (91). To differentiate between constipation and incomplete DIOS can be tricky, but there are some important differences; a right iliac fossa mass should lead the clinician to consider DIOS over

constipation, for example.

2.14.7 Diagnosis of DIOS

DIOS is usually diagnosed clinically. Typically, one can feel a right lower quadrant mass on abdominal palpation and the patient may experience a colicky, progressive pain in the right lower quadrant or peri-umbilical area. If a known CF patient presents with this clinical picture, along with vomiting and abdominal distension, complete DIOS should be suspected (91).

The ESPGHAN CF Working Group defined DIOS as "acute complete or incomplete faecal obstruction in the ileocaecum". They also set out clinical criteria for diagnosing incomplete and complete DIOS, as shown in table 1.3 below:

Table 1.3: Criteria for diagnosing DIOS (102)

ESPGHAN CF Working Group definition for DIOS in cystic fibrosis
No. 1 Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography
No. 2 Faecal mass in ileo-caecum
No. 3 Abdominal pain and/or distension
Complete DIOS: no. 1, no. 2, and no. 3
Incomplete/Impending DIOS: no. 2 and no. 3, without no. 1

a) Differential Diagnosis of DIOS

Surgical pathologies such as appendicitis, intussuseption and volvulus, are also important to rule out as they can also present acutely in similar ways to DIOS (91).

b) Radiological evidence for DIOS

If there is any doubt in the clinical picture, a radiological diagnosis should be sought. In DIOS, the radiograph will show a bubbly, granular mass in the right lower quadrant (116). Air levels in the small intestine may also accompany the mass (123); a CT scan can also be used to confirm the diagnosis if there is some doubt after the plain radiograph.

Examples of DIOS on a plain radiograph and a CT scan are shown below in figures 2.2 (122) and 2.3 (124).

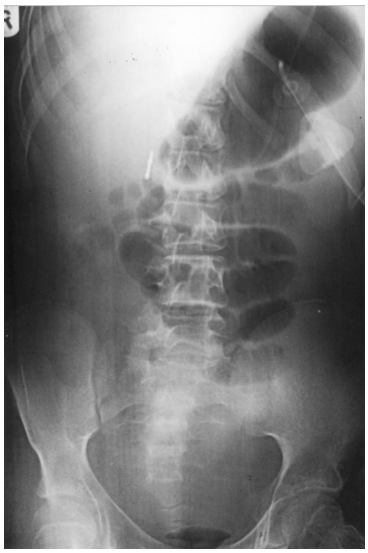


Figure 2.2: Plain radiograph of DIOS with dilated loops of small bowel and shadowing in the right iliac fossa (122).

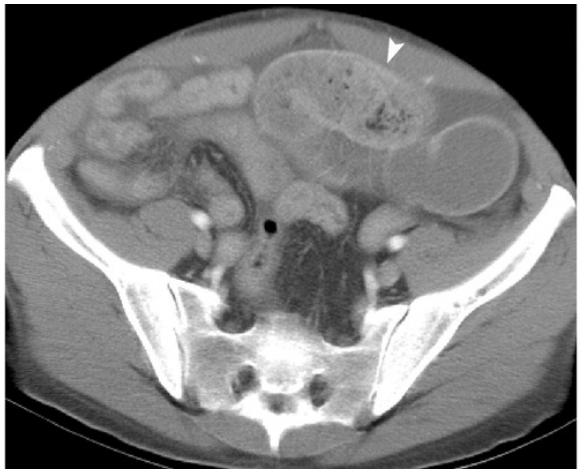


Figure 2.3: CT scan of a 37 year- old man with DIOS. Dilated small bowel loops are seen. White arrowhead shows the bubbly, granular intraluminal contents (124).

2.14.8 Management of DIOS

a) Treatment of DIOS

If a diagnosis of incomplete DIOS is made but the patient is clinically stable, they may respond to one of the laxative regimens described in section 2.14.2. However, if there is inadequate response, other drugs are used. One of these is another type of osmotic laxative, Diatriozate (Gastrografin®). It is given as a single dose, orally or via nasogastric tube, which can be repeated fully or as half-doses every 24 hours. Adult doses range from 30 to 90ml, children aged between 5 and 10 years may take doses of 60ml and children under the age of 5 are recommended to take 30ml (104). Another osmotic laxative given is polyethylene glycol, under the brand name, Klean-Prep®, with the aim to cleanse the bowel. The solution is given until clear fluid is passed per rectum and there is resolution of pain, vomiting and abdominal pain. Children aged between 1 and 17 years may take a dose of 10ml per kg per hour for 30 minutes, which can be increased up to 25ml. This regime is usually given over 4 hours and can be repeated in necessary. Adults may take

one sachet (69g) dissolved in 1 litre of water, which may be taken twice per day. A single dose of oral N-acetylcysteine can also be used to treat DIOS. As a mucolytic, it can help to degrade the obstructing faecal material (91). This is given at a dose of 4 to 6g in older children (7 to 17 years) and 2 to 3g in younger children (2 to 6 years). There are no guidelines for the use of N-acetylcysteine in adults with DIOS, as it is only recommended for children (104).

Complete DIOS is treated in a similar way to incomplete DIOS, but is usually managed in hospital. Furthermore, the patient may be commenced on conventional "drip and suck" management for bowel obstruction: IV rehydration, nil by mouth and nasogastric aspiration. Diatriozate can be administered via enema, but should be done so with caution as fluid shifts in the bowel can lead to shock and perforation (125, 91) The aim of managing complete DIOS is to avoid surgical intervention as much as possible, but this may be necessary if the patient is not responding to medical treatment.

b) Prevention of DIOS

For the prevention of DIOS, it is recommended that patients have adequate hydration and good adherence to pancreatic enzyme therapy. Furthermore, prophylactic laxative therapy is advised if the patient has had a previous episode of complete DIOS or clinical evidence of incomplete DIOS. It may also be used post-operatively for CF patients who have undergone organ transplantation. Prophylaxis can also be given to patients who are pancreatic insufficient and have clinical or radiological evidence of constipation (e.g. palpable faecal masses with abdominal pain) (91).

2.14.9 Summary

DIOS has been discussed in detail in this section. It occurs when thick, sticky mucus produced in the CF intestine combines with viscid faecal material in the lumen of the terminal ileum and/or caecum. It is distinct from constipation in its pathophysiology, but can sometimes be difficult to distinguish clinically. However, the ESPGHAN CF Working Group has provided clinical criteria to diagnose incomplete DIOS and complete DIOS. DIOS is surprisingly common and affects 10-22% individuals with CF. Risk factors include previous episodes of DIOS or meconium ileus, pancreatic insufficiency and non-adherence to PERT.

Aside from measures such as good adherence to pancreatic enzyme therapy and adequate hydration, there is little evidence for any particular laxative regimen. For the prevention and treatment of DIOS, there are many different types of laxatives used in various combinations across the CF centres in the UK. This subject has not been studied in detail and as such, there are no recommendations on the prevention or treatment of DIOS. A systematic review of the literature is required to provide guidance for the management of DIOS. The review may discover that there are gaps in the literature, but if this is the case, it should act as a source of incitement for further research on the subject.

Chapter 3. The Cochrane Systematic Review: An Introduction.

3.1 Defining a Cochrane review

Cochrane reviews are systematic reviews of research on a particular topic. They are considered to be the highest standard of evidence-based health care resources. The Cochrane Collaboration is named after the late Archibald Cochrane, a Scottish doctor who was famous for promoting the use of randomized controlled trials to improve the efficacy and safety of clinical practice. His 1971 book, “Effectiveness and Efficiency” criticized the lack of evidence-based medicine. His work was extremely influential and eventually led to the creation of the Cochrane collaboration in 1993 (126).

Each Cochrane review works by collating and analysing the data and results of relevant studies relating to a specific objective. Before starting a review, the authors must produce a set of strict criteria for inclusion and exclusion of studies. Authors can seek advice from the Cochrane Review Group (CRG) in their particular speciality. The relevant, included studies are combined and put through a detailed process of data extraction and statistical analysis to give an overall result. This should decide whether the combined study results provide statistically significant, good quality and reliable evidence on the chosen topic (127).

3.2 Motivation for the Cochrane review

Distal intestinal obstruction syndrome is a major problem in CF, as discussed in Chapter 2. Incomplete DIOS is common (102) and therefore it seems rational that there should be

recognised guidelines for its management. However, anecdotally and as demonstrated by the results of the consultant survey (see chapter 5), there is much variation in clinical practice.

There are some general guidelines about the prevention and treatment of DIOS, although they do not have a high quality evidence base. For preventative measures, adequate hydration and good adherence to pancreatic enzyme supplementation is recommended, as well as prophylactic laxative therapy for patients who have had a previous episode of complete DIOS. Maintenance laxative therapy may also be given to patients with incomplete DIOS or for those with clinical or radiological evidence of constipation (see section 2.14.2) (91). For the treatment of DIOS, various laxative regimens can be used, but there are no absolute recommendations. In some cases, medical management may fail and the patients will have to undergo surgery. This is seen as a last resort, as it dramatically increases the risk to the patient (128). By conducting Cochrane reviews to investigate the current management strategies for DIOS, I aim to determine the aperients that are supported by the best evidence and secondly, identify important gaps in the research. By alerting clinicians to gaps in the literature, it may encourage further research on the topic.

It is also important to note that individuals with CF experience a significant treatment burden. A review should address this by discussing the risks and benefits for various laxative agents and give information on their potential adverse effects and tolerability.

3.3 Starting a Cochrane review

3.3.1 The Protocol

Before starting a Cochrane review, one must first publish a protocol. The protocol acts as a scaffold for the review and includes the essential information on which to base the review. Sections of the protocol include the background, objectives and methods. The background section describes the condition and intervention, how the intervention might work and why it is important to do the review. The objectives section should include a primary question or outcome. The methods section outlines the selection criteria for studies, search strategies and overview of the process for data collection and analysis. The protocol should be set out clearly, according to the guidelines in the Cochrane handbook (129). It should also be relatively easy to read so that non-experts can understand it.

There are a few reasons why authors must produce a protocol. Firstly, discussing strategies prior to the review promotes transparency and reduces risk of bias from the authors. For example, by setting the criteria for inclusion of studies in the protocol, it reduces the risk of inclusion of studies that are not suitable but may have a favourable outcome that support the authors' hypothesis. A protocol also ensures that peer review of the methods is possible, which can help to improve the quality of the review. Furthermore, publishing a protocol reduces risk of duplication (130, 129).

Publishing a Protocol

Due to the high standard, systematic approach of Cochrane reviews, it is usual for reviewers to receive a number of recommendations from the CRG before a protocol is published. The CRG must ensure that the reviewers' protocol is relevant, thorough and transparent.

Initially, the CRG reviews a protocol and if there are improvements to be made, it is sent back to the authors with recommendations. Once the review group has no more recommendations for the authors, the protocol is then forwarded to the contact editor and co-editor for approval to publish.

3.3.2 Use Of Software

The software program used by authors to write and update Cochrane reviews is Review Manager 5.3® (RevMan 5.3®) (131). It is also used to help prepare the protocol and comes with a set of headings and subheadings to prompt the user. The Methodological Expectations for Cochrane Intervention Reviews, or "MECIR" guidelines can be activated on the program to help the user include all the relevant sections in the protocol. The Cochrane Handbook also provides useful and detailed guidance. When it comes to writing a review, RevMan® facilitates the preparation of study characteristics, comparison tables and study data. Furthermore, RevMan® can perform meta-analysis of data and present the results in graphs (132).

3.3.3 The Review Team

The process of writing a Cochrane review demands teamwork. At least two authors are required for the process of screening studies and data extraction. This must be done independently to reduce the risk of bias and error. To give an example of how our team worked for the review, "Interventions for the prevention of DIOS", WC and I independently screened studies for inclusion or exclusion. Then the third author, FG,

acted as an arbiter to review any disagreements we had. This process and the process of data extraction will be described in more detail in Chapter 4.

Ideally, one of the members of the team should already have some experience in Cochrane review methodology. We were fortunate that WC had attended the advanced training courses at Cochrane and had experience in statistics. It is also recommended that one member of the team should be an expert in the area being reviewed. FG had a great amount of clinical experience in CF, so was therefore appointed as the main source of clinical knowledge.

Our team also extended to members of our Cochrane Review Group (CRG), the Cochrane Cystic Fibrosis and Genetic Disorders Group. CRGs are made up of experts in Cochrane reviews who offer support, information and guidance for authors. Two members of our CRG who particularly assisted us in creating the protocol and review were NH, an information specialist and NJ, the managing editor.

3.3.4 Cochrane Review Training

Although the Cochrane Handbook and CRG provide very useful information, first-time reviewers are encouraged to complete training courses. To improve my understanding, I attended the four-part training course at the UK Cochrane Centre in Oxford.

The Review Author (RA) training courses are grouped into two main parts. RA1 and RA2 (attended 18-19th October, 2016) are designed to help authors construct their protocol and RA3 and RA4 (attended 15-16th February, 2017) address the methodology, analysis and reporting of systematic reviews. The courses greatly improved my understanding of how to write a protocol and the main steps involved in generating a Cochrane review. The

certificates of attendance from the Cochrane Review Author training courses can be found in Appendix 6 of this thesis.

3.3.5 Types of Interventions for DIOS

The management of DIOS is divided into the treatment of DIOS and the prevention of DIOS, so I undertook two separate Cochrane reviews to investigate the evidence base for these two areas of management. The indications and main outcomes for prevention and treatment are different; therefore separate reviews were required. Furthermore, although laxatives are used for both treatment and prevention of DIOS, there would most likely be differences in the type of laxative used, as well as the dose and the route of administration. In the next chapter, I will discuss the Cochrane review on the Interventions for the prevention of DIOS. In chapter 5, I will discuss the Cochrane review on the Interventions for the treatment DIOS. I will aim to meet the first objective of this thesis by describing and explaining the methods used to conduct these systematic reviews. I will explain the criteria for inclusion of studies, descriptions of the medical databases used, the search strategy and search terminology used. I will also describe the process of data extraction and the methods used to analyse the data.

Chapter 4: Cochrane Systematic Review on the Interventions for Preventing DIOS in CF.

4.1 Objective

- To assess the effectiveness and safety of different groups of laxative agents for preventing distal intestinal obstruction syndrome (incomplete and complete) in children and adults with CF.

4.2 The Protocol

The protocol had to be designed before the academic year started so there would be enough time to complete the review. Therefore, WC initially drafted the protocol. The CRG then sent the protocol back with advice for improvement. After I completed the first part of the Cochrane training course, I contributed content and references to sections describing the condition and intervention. I then assisted WC in editing parts of the methods section (e.g. the outcomes measures, search methods and measures of treatment effect).

Our final submission of the protocol took place on 27/02/2017 and it was published on 11/04/2017. It can be found in **Appendix 2** of this thesis.

4.2.1 Writing the protocol

It is recommended that authors should write the protocol for a review using the PICOS criteria, an abbreviation for, “Participants, Intervention, Comparison, Outcomes and Study design” (129). These criteria should be set out in every protocol and are expanded to establish clear guidelines for the inclusion or exclusion of studies in the review. This facilitates the process of study screening and data extraction.

In the sections below, I detail these criteria:

a) Participants

Distal intestinal obstruction syndrome is specific to patients with CF, so I required the participants to have CF, diagnosed by either sweat test or genetic testing. Although it is usually more common in adults (8), children can suffer from DIOS too. Therefore, I searched for studies including children and adults with CF (with all stages and severity of lung disease and with or without pancreatic sufficiency).

b) Intervention and Comparison

i) Types of interventions

Laxatives form the basis for the prevention of DIOS. We (WC, FG and I) agreed that I should investigate laxatives as the main intervention for this Cochrane review.

ii) Categorising the difference types of laxative

I decided to group the laxatives according to their main mode of action. I ultimately arrived at 3 main categories of laxative: osmotic agents, stimulants and mucolytics.

Osmotic laxatives act as stool softeners. They exert an osmotic effect in the lumen of the large intestine and either cause a fluid shift from the body to the bowel, or prevent fluid from leaving the bowel (104.). In DIOS, osmotic laxatives may soften the viscid stool (caused by the combination of mucus and faeces) that has accumulated in the bowel.

Stimulant laxatives are effective are stimulating peristalsis (104) so could reduce gut transit time and prevent mucofaeculant material from adhering to the bowel wall. As depicted in the name, Mucolytics work by disintegrating the mucus produced in CF. They could therefore prevent the combination of faeces and mucus or breakdown existing mucofaeculant material.

There are various medications that fall into the 3 categories of laxative. These are described in **Appendix 2.**

During the process of categorising the laxatives, it became evident that some drugs have more than one mechanism of action (e.g. Macrogrol 3350 is an osmotic agent with stimulatory effects). To avoid confusion, I would primarily compare any laxative therapy to a control or no treatment. Thereafter, I would assess the relative effectiveness of laxative agents in a subgroup analysis. For the purpose of the protocols, I categorised agents with more than one mode of action according to their main mechanism e.g. I listed sodium docusate as a stimulant, but it also has stool softening properties.

iii) Types of comparisons

I decided to compare various laxative therapies at any dose to placebo, no treatment or alternative laxatives for the prevention of DIOS. I would evaluate the effectiveness of

laxatives at any dose in order to comprehensively assess the therapeutic range of different aperients. For example, high doses may cause adverse effects such as flatulence, abdominal pain, diarrhoea or soiling. Knowing the risk of these effects would be useful in future clinical practice for titrating patient doses.

c) Outcomes

Reviewers must compile a list of main outcomes they deem to be most relevant to the review's objective. There should be a maximum of 7 outcomes, each one reflecting an important part of the decision-making process for patients. Because of this, many intervention reviews share similar outcomes. Common outcomes include adverse effects, survival, clinical events (e.g. complete bowel obstruction) and quality of life. Outcomes are central to the review, not only because they are used to judge the effectiveness of the intervention, but also because they are used to construct the "Summary of Findings" table at the end of the review. This table presents the main conclusions of the review in a clear and concise manner.

When it comes to the process of screening studies, outcomes are not usually part of the eligibility criteria for including studies. As mentioned, they are used to judge the effectiveness of the intervention in question. Instead, the reviewers should include studies that match the rest of the eligibility criteria i.e. participants, intervention, comparison and study design (129).

i) Primary outcomes

Primary outcomes are chosen from the list of main outcomes. There should be a maximum of 3 and as suggested in the title, they are the most important outcomes for

assessing the intervention of a review. It is strongly advised that reviewers include at least one “undesirable” outcome in their list of primary outcomes (129).

I aimed to assess the following primary outcomes for the review, “Interventions for the prevention of DIOS”:

1. Complete or incomplete DIOS diagnosed either clinically (e.g. abdominal masses, or distension or pain) or radiologically (e.g. dilated bowel or faecal mass).
2. Adverse effects from treatments

    i) Serious adverse effects of treatment regimens (including, but not limited to, rectal bleeding, intestinal perforation, mucosal erosions, anaphylactic reaction, vomiting with electrolyte disturbance)

    ii) Other adverse effects of treatment (e.g. diarrhoea or soiling, abdominal distension, loss of continence or pain)

1. Clearly, the diagnosis of DIOS is a significant clinical event for this review, as its main objective is to assess laxatives for their effectiveness in preventing DIOS.

2. As previously mentioned, adverse effects are commonly used as outcomes for intervention reviews. They are important in evaluating the safety of an intervention. Assessing the safety of different aperients was stated in the review’s objective and so it is fitting that, “adverse effects from treatments” is listed as a primary outcome.

Information on adverse effects can be gathered in different ways. One may either consider the range of adverse effects per person, or the range of adverse effects for all

the participants in the study. For our reviews, I would assess the adverse effects across the whole study. Reviewers should also state whether they are assessing the severity or seriousness of adverse effects. Severity of adverse effects is similar to intensity. The severity may be mild, moderate or severe. An example of an adverse effect measured in severity would be abdominal pain.

On the other hand, serious adverse effects include those that could be dangerous or even fatal. I would assess these in our review. Examples of serious adverse effects from laxatives are listed above i.e. rectal bleeding, intestinal perforation.

ii) Secondary outcomes

Secondary outcomes are also taken from the list of main outcomes. They are not as significant for clinical decisions as primary outcomes are, but help to make the review more comprehensive in assessing the effectiveness of an intervention.

I aimed to assess the following secondary outcomes for the review, "Interventions for the prevention of DIOS":

1. Time to hospital admission

    i) All causes

    ii) Due to DIOS

2. Patient-reported quality of life (QoL) scores
3. Patient-reported symptom scores
4. Tolerability (participant- or investigator-reported rates of concordance)

The first secondary outcome for this review is a time-to-event outcome (133). Patients with complete DIOS are acutely unwell, so they are usually admitted to hospital in this situation. This outcome may therefore be useful for determining the effectiveness of a laxative regimen in preventing complete DIOS. I separated the outcome into two points, because patients with CF may be admitted to hospital for various reasons other than DIOS e.g. respiratory tract infections.

The next three secondary outcomes are related to patient experiences. Patient reported outcomes measures (PROMs) are often useful when objective outcomes are not available, or for complementing more objective outcomes (e.g. diagnosis of DIOS) as they come directly from the patient without influence from clinicians or study investigators. PROMs offer the patient's perspective on the treatment and may alert investigators to flaws in the treatment that cannot be picked up by objective markers. For example, a treatment may demonstrate great efficacy and have a low adverse effect profile, but the patient may feel as though the treatment burden has an impact on their quality of life. PROMs are key for delivering the patient-centred care that is practiced in medicine today. They may be collected in different ways, though diaries, questionnaires and interviews are commonly used (129).

d) Study Design

As these were intervention reviews, the most suitable studies to use were comparative studies, as they would evaluate the differences between a control and intervention. The highest quality comparative studies are randomised-controlled trials (RCTs). RCTs are the best studies to judge the effectiveness of an intervention because they randomly allocate participants (e.g. by a computer generated random sequence) to a group. This means that

the demographics and characteristics of participants are not taken into account. Each participant has an equal chance of being chosen for the intervention. RCTs therefore minimise the risk of selection bias and generally provide more reliable evidence for interventions than other types of studies.

After discussion with my supervisors, I also chose to include quasi-RCTs. These are comparative studies, but allocate participants based on known criteria, such as date of birth or alternation (e.g. Monday's patients receive intervention, Tuesday's patients receive control). Unlike RCTs, participants are not assigned to groups through concealed randomisation. This may pose a problem if clinicians are aware of the sorting process. For example, they could potentially ask the sickest patients to come in for clinic on the day that participants are receiving the intervention. Quasi- randomisation runs the risk of manipulation of the selection process, which can imbalance the baseline characteristics of participants, leading to unreliable results. Therefore, I planned to assess quasi-RCTs on their merit using the Cochrane risk of bias tool. I would only include a quasi-RCT if the second reviewer and myself were satisfied that the intervention and control group were similar at baseline (134).

After discussion with WC and FG, I also decided to assess crossover trials for inclusion in the review. In crossover trials, all participants follow a succession of interventions, rather than being allocated to parallel groups (such as in an RCT). For example, participants could be sorted into two groups. Group A takes the intervention and Group B takes the control. After a period of time, the groups switch so that the intervention group now takes the control and vice versa. This means that all participants experience the control and intervention. Crossover trials can therefore be useful in determining individual

comparisons, which removes baseline variations that are in parallel group trials. However, there are also weaknesses in this model. The main downside is that the effects of the intervention could be carried over to the control group. This could influence the treatment effect and increase the risk of bias. (134).

4.3 Search methods

NH, a Cochrane information specialist, designed the search strategy for the review. During the screening process I decided to accept titles and abstracts that matched the eligibility criteria for the review. In this section, I will describe the medical databases and online registries used to search for studies, as well as the search terminology and syntax used in the search strategy. I will also describe the screening process and include details about the software used to screen the studies.

4.3.1 Medical databases

I searched the following online databases for relevant studies to be included in the Cochrane systematic review:

- Cochrane Central Register of Controlled Trials (CENTRAL) (135): This database is part of the Cochrane Library and is updated quarterly. It is frequently used to run searches for trials and studies to be included in Cochrane reviews. It contains the highest number of reports of controlled trials. As of January 2008, CENTRAL contained nearly 530,000 citations suitable for Cochrane reviews. 310,000 trials reports are from MEDLINE, 50,000 are from EMBASE and 170,000 are derived from other databases and handsearching (129).

- MEDLINE: This bibliographic database has very broad subject coverage, containing citations from over 5,600 journals worldwide. It is the main database used by the US National Library of Medicine ® (NLM) and is all-encompassing in the subjects of biomedicine and health. It includes literature outside the reaches of clinical medicine, for example: life sciences (such as plant, marine and animal biology), behavioural and chemical sciences and bioengineering. The NLM indexes the records in MEDLINE with Medical Subject Headings (MeSH), which is a unique feature of the database. MEDLINE was searched from 1946 to present, using Ovid as a search engine (136, 129).

- EMBASE (Excerpta Medica Database): This database contains a wide array of pharmaceutical and biomedical information, with over 2,900 journals that cannot be found at MEDLINE. EMBASE is particularly useful when looking at drug efficacy, drug-disease relationships, drug-drug interactions and adverse events. It also uses its own thesaurus called EMTREE, which indexes all of the EMBASE content. It contains a much higher number of synonyms and terms than MeSH (from MEDLINE) and a more extensive drugs facet (137, 129). EMBASE was searched from 1974 to present, using the Healthcare Databases Advanced Search (HDAS) tool.

4.3.2 Electronic searches

I also searched the following online registers and resources for relevant studies:

- Cochrane Review Group Specialist Register: The relevant studies were searched for from the Group's Cystic Fibrosis Trials Register using the term: distal intestinal

obstruction syndrome (DIOS). The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective hand-searching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference (138, 129).

- US National Institutes of Health Ongoing Trials Register- Clinicaltrials.gov. This is a registry and results database containing details about clinical trials involving humans around the world. One can search for proposed, ongoing and completed studies. According to the most recent website figures (17/04/2017), the registry lists 241,812 studies (139).

- International Standard Randomised Controlled Trial Number (ISRCTN) Registry: This is a clinical trials registry that provides each trial with a unique identifying number. The number is used to keep track of reports and publications related to the trial. ISRCTN features trials that assess the efficacy of a health intervention in a human population, incorporating both observational and interventional trials (140).

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP): The main aim of the WHO ICTRP is to facilitate the registration of clinical trials to make them accessible to the public. The search portal provides a single point of access to these ongoing and completed trials that adhere to WHO standards (World Health Organisation (141).

- Open Grey: This is a resource containing 700,000 bibliographic references of grey literature (paper records) produced in Europe. It is an open access website, so the records can be easily located and exported. Grey literature includes sources such as research reports, doctoral dissertations and conference papers, among others (142).

I searched these main medical databases and registries on the recommendation from NH in order to obtain extensive information on the current practices for the prophylaxis of DIOS. As a minimum, it is recommended that CENTRAL and MEDLINE are both used to run searches for Cochrane Systematic Reviews. EMBASE is also recommended, if available to the Cochrane Review Group (CRG) or review author (JG) (129). As per the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guideline (143), NH advised that clinicaltrials.gov and WHO ICTRP were searched too. Ongoing trials are important to identify, so that they can be later assessed for inclusion in the updates of the review.

4.3.3 Search strategy

a) Search methods for identification of studies

I searched all relevant published and unpublished trials using the search strategy devised by NH, without restrictions on language or publication status. Details of the search strategies used can be found in **Appendix 1.**

b) Search terminology:

I identified search terms with the aid of NH. The search terminology was based on the eligibility criteria for the review as outlined in the protocol.

i) Condition of interest: The condition was CF. I also searched other terms for cystic fibrosis in order to retrieve a higher number of studies. I also included the abbreviation of cystic fibrosis, "CF", as well as "mucoviscidosis" and "fibrocystic". The latter refers to fibrocystic disease of the pancreas. Both terms were used to describe CF in the mid 20th century (7).

ii.) Outcome of interest: The main outcome for the reviews was distal intestinal obstruction syndrome. I also searched the abbreviation, "DIOS", as well as descriptive terms for the condition, such as "faecal obstruction" and "faecal impaction". I searched the subject headings, "intestinal obstruction" and "constipation" and then "exploded" these to include more specialised terms in the search. I also included the historical name for DIOS, "Meconium ileus equivalent" or "MIE" (105)

iii.) Interventions of interest: The potential interventions for this review were osmotic laxatives, stimulant laxatives, mucolytics and laxatives with more than one mode of action. I searched the index term, "Laxatives" and exploded it to retrieve more definitive terms. I also searched individual names of laxatives. In order to obtain more results, I used both generic and brand names of drugs e.g. "polyethylene glycol" and "Movicol®".

c) Search Syntax

I searched thesaurus terms in the databases that had an indexing system (CENTRAL, MEDLINE and EMBASE) to identify relevant results that could be labelled as different terms. I did this by writing "MeSH descriptor" after a word or term in the CENTRAL system, e.g. "Laxatives *[Mesh descriptor]*", or by adding a forward slash (/) after the term e.g. "Laxatives/" in MEDLINE and EMBASE.

I also used extensive truncation in the medical database strategies. This is a technique used to obtain all possible suffix variations of the word in question, e.g. “constipate$” or “constipate*” could retrieve terms such as constipated, constipation or constipating.

I used the Boolean operators (144) “AND” and “OR” to improve the search strategy. Combining terms using “OR” resulted in a broader set of results. This was implemented for each component to ensure that all synonyms of a term e.g. “cystic fibrosis” or “distal intestinal obstruction syndrome” were accounted for. The operator, “AND”, was used to narrow the results in the search strategy. This was used at the end of each search. The terms for the outcome and intervention were combined to retrieve more specific and therefore, more relevant results.

To include results in which two desired words would appear next to one another, I used the command, “adj”, e.g. “(faecal adj (obstruction or impact*)). This means the word, “faecal” should appear next to either “obstruction” or “impact*” in a phrase. This command can be expanded to include words that appear near each other but not necessarily next to one another. For example, “(faecal adj3 (obstruction or impact*))” means two additional words are permitted between “faecal” and either “obstruction” or “impact*”.

d) Issues with syntax

I planned to search EMBASE using Ovid as a search engine, but due to problems with access to the system, I had to use Healthcare Databases Advanced Search (HDAS) instead. On the advice of NH, I altered the search syntax to accommodate this change. For

example, “tw”, meaning title or abstract in Ovid, was changed to “af”, meaning “all fields” in HDAS. The truncation symbol, shown as the dollar sign ($) in EMBASE Ovid, had to be changed to an asterisk (*) for EMBASE HDAS.

4.4 Data collection and extraction

4.4.1 Selection of studies

a) Use of software

After entering each search strategy into the relevant database, I then exported the search results (titles and abstracts of the studies) onto an online software program called Covidence© (145). Reviewers use Covidence© for organising and screening studies. It also facilitates the process of data extraction, the risk of bias assessment and exports data and references into RevMan®.

I imported citations from CENTRAL, MEDLINE, Embase, ISRCTN and Open Grey onto Covidence©. Citations from WHO ICTRP and clinicaltrials.gov could not be imported onto Covidence©, so I uploaded the citations manually and created a hyperlink for each one so that the other reviewers could view the clinical trial online.

b) De-duplication of studies

When I exported the citations to Covidence©, it automatically removed a 588 duplicates. However, Covidence© can only remove very precise, identical citations, so some duplicates remained and were included in the screening of titles and abstracts.

c) Screening studies

The first stage of the screening process is to select relevant titles and abstracts that can be included in full-text screening.

WC and myself screened the titles and abstracts independently. Covidence© is set up so that each reviewer simply votes, “yes”, “no” or “maybe” for each. If both reviewers vote “yes” or “maybe” for a study, it is then taken to full-text screening.

If both reviewers vote “no” for a study, it is simply listed as “irrelevant” and excluded from the review. When WC and I voted differently for a study, it was flagged up as a “conflict” on Covidence©. In these situations, FG acted as an external arbiter to have a final say on whether the study should go through to full-text screening.

Most imported citations included titles and abstracts of the studies, but some only included the title. It was usually clear from the title whether or not the study was relevant to either review (e.g. respiratory intervention studies were excluded). If it was not clear, I could hand-search for the abstract online. In some circumstances, the title was very vague and no more information could be found elsewhere. In 5 cases where we could not rule out the study, it had to be included in the full-text screening process.

d) Examination of full text reports

After FG resolved the conflicts from the title and abstract screening, we initially had 9 citations to go to full text screening. However, one study was duplicated on Covidence©, so there were actually 8 different studies to assess for inclusion or exclusion.

More details about the results of the searches can be found in the Results section later in this chapter.

e) Reference Lists

I checked the bibliographies of relevant studies to identify further references to appropriate trials. I screened these studies according to the eligibility criteria applied to the other titles/abstracts.

4.4.2 Data extraction

Data extraction is very important in a Cochrane review. Essentially, the reviewers carefully examine full-text versions of studies (usually in the form of reports or articles from journals) (129) to determine their eligibility for inclusion in the review.

Paper data extraction forms were provided to us by our CRG. Covidence© also provides an electronic tool for data extraction. I used the paper form to obtain the basic information for each study, and then entered the data onto the more detailed form online.
Data collection and extraction offers a useful summary of all the important criteria that is relevant to the review. On the paper form and electronic form, there are prompts to ensure that reviewers are aware of the information that needs to be extracted. Secondly, they provide a record of the thought process and decisions made during data extraction, which can be useful to refer back to during the write-up of a review. But perhaps most importantly, data collection forms provide data that will be analysed in the Cochrane review (146).

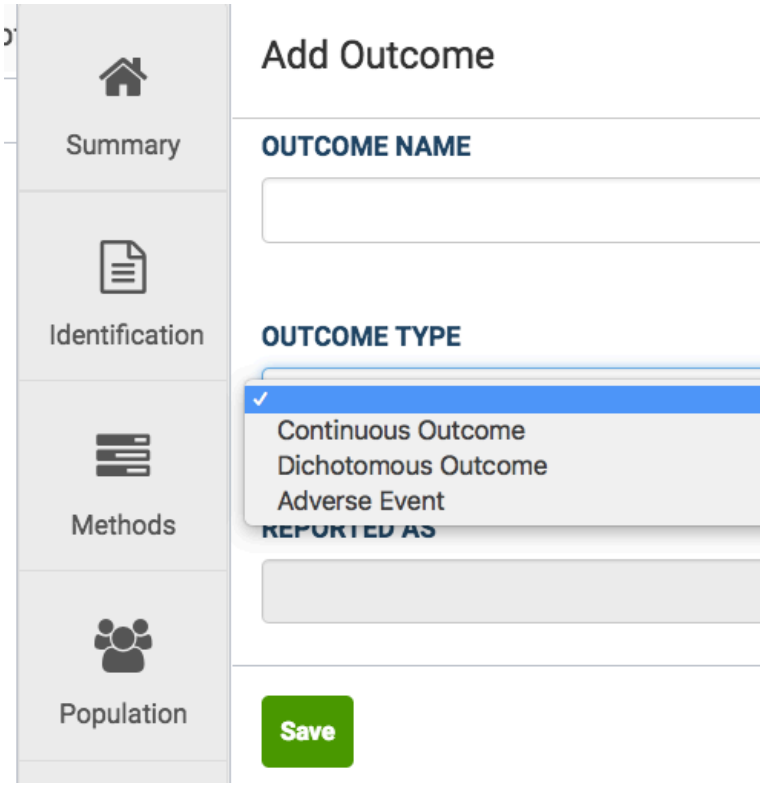
If we decided that a study did not have a relevant design, participants or intervention(s), it would be excluded from the review. For studies with unclear outcomes, we would try to contact the trial authors for more information. During this time, it would be listed as "awaiting assessment". If there were no clarification regarding the outcomes after 3 attempts at contact, the study would be excluded.

It is recommended that more than one reviewer should be involved in the data extraction process. WC and I independently used the data extraction tool on Covidence© for each study. Then we compared our forms for discrepancies and discussed these in order to arrive at a final decision. FG also acted as an external arbiter for any disagreements we could not resolve with discussion.

After extracting data from studies, I entered it into RevMan® for analysis.

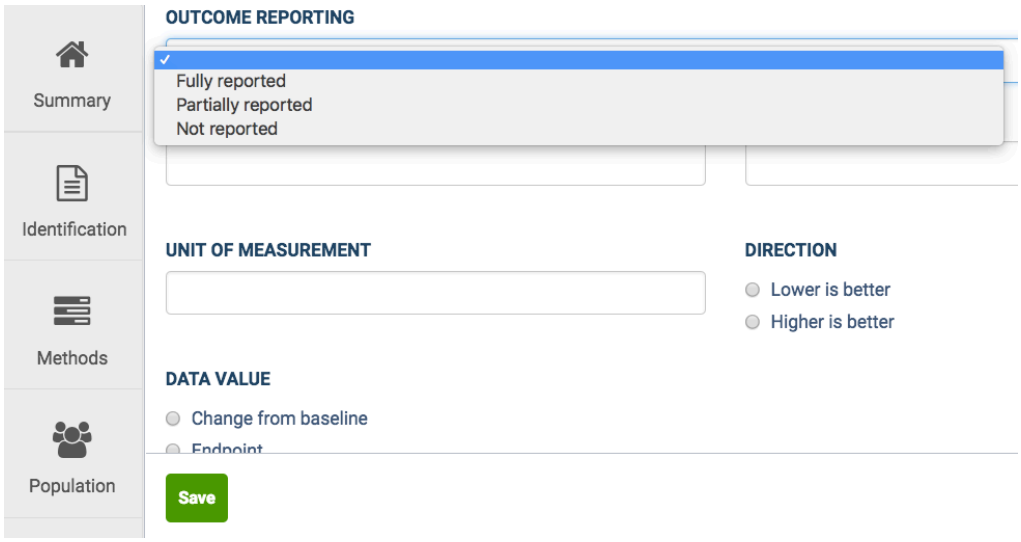
The figures below are screenshots demonstrating the data extraction forms on Covidence©:

Figure 4.1: Screenshot 1 of the outcomes section on a Covidence© data extraction form.



The bar on the left hand side (Identification, Methods, Population) shows the other main areas covered in data extraction. Covidence© prompts the user to select an outcome type for each outcome so that the measure used is correct.

Figure 4.2: Screenshot 2 of the outcomes section on a Covidence© data extraction form.



This figure illustrates the various ways to classify and detail each outcome.

4.5 Data analysis

In the next sections, I will describe the tools and methods used for analysing the study data. Each section directly relates to a step briefly described the protocol **(Appendix 2)**. However, I also aim to include definitions and explanations of the methods in each section, using my knowledge from the Cochrane training courses and guidance from the Cochrane Handbook (129). The different methods include assessing the risk of bias, measuring the effects of treatments, unit of analysis issues, dealing with missing data, assessing heterogeneity, subgroup analysis and sensitivity analysis.

4.5.1 Assessment of risk of bias in included studies

a) Types of bias

There are main 6 categories of bias that can be found in studies: selection bias, performance bias, detection bias, attrition bias, reporting bias and other types of bias (147). It is essential for authors to carefully assess the risk of bias for each study, so that the review provides reliable information.

Selection bias is assessed by the how the participants were allocated to either the placebo or intervention. For a low risk of bias in this category, the study should describe random sequence generation (e.g. by computer generated randomisation) and concealed allocation (e.g. giving participants opaque, sealed envelopes) so that the investigators do not know what the allocation will be.

Performance bias is related to the blinding of those involved in the study (the participants and personnel). Low risk of performance bias may be described in studies as “double-blinding”, meaning that both personnel and participants had no knowledge of the intervention administered or received.

Detection bias is related to the blinding of outcome assessors for an intervention. This is low risk if the study described “blinding” or “masking” of the outcome assessors to the type of intervention each participant received.

Attrition bias occurs when there is incomplete outcome data resulting from withdrawals in a study (e.g. due to adverse effects or loss of follow-up). If the study has described reasons for these missing data and included an intention-to-treat (ITT) analysis, the risk of bias may be low in this category. ITT analysis simply means that all participants were analysed as per their randomised groups, even if some had dropped out or been excluded before the end of the study.

Reporting bias means that the study has selectively reported outcomes, rather than reporting all the outcomes that were measured. It is useful to have access to the study protocol in order to judge this, as we can directly compare the outcomes listed in the protocol to those reported in the study.

b) Assessing Bias for each study

I used the Cochrane Risk of Bias Tool to assess the risk of bias in the six domains described above. Covidence© provided accessible and simple software to facilitate this. Independently, WC and I ranked each of the domains, “high”, “low” or “unclear”, depending on the description in the study. For each ranking, we added comments to justify our decision. After we had completed the assessment, we compared our

judgements, resolved our disagreements with discussion and came to a consensus. We initially had conflicting views on the risk for the domain of selection bias and detection bias; WC ranked these domains as having a low risk of bias, but I ranked them as having an unclear risk of bias. We came to an agreement after discussion amongst ourselves and with FG's opinion. I will explain our final decision and how we arrived at this conclusion in the Results section later in this chapter.

4.5.2 Measures of treatment effect

a) Types of outcome measures

There are two main types of standardised outcome data described in the Cochrane handbook: dichotomous and continuous (148).

i) Dichotomous data

Dichotomous data can have one of two outcomes. For example, a patient either has complete DIOS or does not have complete DIOS. The dichotomous treatment measures are described in the protocol, **Appendix 2.**

Dichotomous data are expressed as the chance of an outcome occurring and is measured in risk or odds. Risk is commonly used in healthcare because it can describe the chance of adverse outcomes. It can be expressed as a decimal between 0 and 1 or a number per 1000 people. For example, the risk of a patient developing complete DIOS may be 0.2, or 200 per 1000 patients.

For measuring the difference in risk between two groups of patients (risk of outcome with intervention versus risk of outcome with control), risk ratio (RR) is used. This is purely

written as a decimal between 0 and 1, but may be converted into a percentage. For example, the RR of complete DIOS in the control group may be 0.6 (60% risk of patient having complete DIOS).

In the review, I measured dichotomous outcomes using the RR with 95% confidence interval (CI), or 99% CI for individual adverse effects. A 99% confidence interval was used for this outcome because I wanted to increase the certainty of the effect estimate. Having a 99% CI means that if the study were repeated any number of times, the CI containing the true effect would appear in 99% of those times. In clinical terms, a healthcare provider would rather be 99% sure than 95% sure that an intervention would not cause an adverse effect that could harm the patient. Healthcare providers and patients rightfully regard adverse effects as very important aspects of medications because they have the potential to negatively impact the patient's quality of life, adherence to treatment and in serious cases, can compromise the patient's safety.

ii) Continuous data

Continuous data can take any value in a specified range, for example, height and weight. We decided to record quality of life and symptom scores as continuous data. When expressing continuous outcomes, the best measures to use are mean value and standard deviation. However, if comparing two groups in a study (the control group versus the intervention group), mean difference (MD) and standardised mean difference (SMD) are often used.

MD measures the absolute difference between the mean values of two groups, where 0= no change. Here is an example: If the mean change in quality of life score for the

intervention is +0.3 and +0.1 for the control, the MD will be +0.2. It is important to be aware of the direction of the scale in MD. A higher score is better for quality of life, but for a negative outcome like pain, it is not. In this instance, a MD of +0.2 would indicate that patients taking the intervention scored 0.2 points higher on the pain scale.

I aimed to use MD with 95% CI to measure the effect of treatments. However, if the study used different scales to measure the same outcome and there was no way to change the unit of measurement, I would use SMD. The SMD is used as a summary statistic in a meta-analysis when the same outcome is measured in the included studies but done so in different ways. For example, quality of life could be measured using different scoring systems. SMD takes the difference in mean outcome in the groups and divides it by the standard deviation of the outcome among participants. This means that it uses the variability seen in each study to express the size of the intervention effect.

iii) Time-to-event data

I aimed to use time-to-event data for time to hospitalisation. This is expressed differently to standardised data. Hazard ratios (HR) are often used to measure survival data or time-to-event data. This is because they describe how fast or slow a particular group will progress to the event. In a HR, a score of 1 means that there is no difference between the control and intervention, >1 favours the intervention and <1 favours the control. If there is a HR of 2, it means that twice the number of patients in the intervention group will progress to the event than the control group in an allocated period of time.

For time-to-event data I planned to calculate the hazard ratio (HR) with 95% CIs using the generic inverse variance method (GIV) on RevMan®. GIV can be used for any summary

statistic and as suggested in the name, it uses the inverse of the variance (with "variance" implying how far the data varies from the mean) to combine the studies together. Each study is represented according to the inverse of their variance. This means that larger studies are given more weight than smaller studies, as the larger the study, the smaller the standard error. The objective of this method is to increase the precision of the presented data in the review (148**,** 149, 150).

b) Collecting data for outcome measures

Using the data extraction tool on Covidence©, I collected the data on outcomes from the studies. For each, I specified whether it was measured as a continuous or dichotomous outcome, then stated how it was reported e.g. standard deviation, standard error or with a confidence interval for continuous outcomes. For each outcome, Covidence© also prompted me to state the unit of measurement (e.g. kilograms) and range (e.g. 1-100) if the information in the study was available. Outcomes that were not reported as continuous (mean with SE, SD or CI), dichotomous (number of events, percentage of events, ratios with CI) or adverse events (number of events, percentage of events, ratios with CI) could be customised. For example, if a p-value was the only result available in the report, I could create a tailored table to input the values. However with the current Covidence© software, custom measures can only be directly exported to Excel, not RevMan®.

4.5.3 Unit of analysis issues

Unit of analysis issues are relevant when the included studies do not follow the simple, parallel trial pattern (where participants are individually randomised into two groups and outcomes are measured from each participant as single measurements) (149). Crossover trials may present unit of analysis issues if the investigators have not accounted for the carry-over effect of treatment from one phase to another, or if the participants have not been sufficiently randomised.

If there were evidence of a carry-over effect so the participants differed from their initial state, I would exclude the trial unless the data from the first phase was available. In these cases, I may have to ask for additional information from the authors. However, it should be noted that using first-phase data only not always recommended, as it takes away the benefit of using a participants as their own controls (151).

There may also be unit of analysis issues in studies where there are multiple treatments compared to placebo and compared to one another. In these cases, I planned to compare each treatment to placebo first and then undertake a subgroup analysis to compare the relative efficacies of each treatment. This is also described in section 4.5.8 below.

4.5.4 Missing data

a) Types of missing data

For missing data, it is important ascertain the reason(s) for their omission. The data may be “missing at random” for reasons completely unrelated to the assessment of that data. For example, if a participant insufficiently completes a symptom score questionnaire

simply because of busy work schedule, it is probably not related to the data being measured.

However, if that participant does not complete the symptom score questionnaire due to adverse effects from the treatment, the missing data may be related to the assessment or data measured. In these cases, the data is referred to as "not missing at random".

If data is "not missing at random" it may be related to selective reporting bias, attrition bias or publication bias. Publication bias occurs when the publication of studies depends on the outcome or the overall treatment effect shown in the results. In these situations, the data from published studies is very different to data from unpublished studies (152).

b) Dealing with missing data

To avoid the issues that can occur from missing data, reviewers must take steps to ensure that any existing published results are found. We would try to contact the investigators (3 times at the most) if there were missing data in the study or if it was unclear how the data were analysed.

Missing participants may be accounted for by an ITT analysis, which should preferably be done by the study authors. In cases where there is no ITT analysis but there are clear records of participants throughout the study, I planned to undertake an ITT analysis myself.

I also planned to undertake a sensitivity analysis (described in below section 4.5.8) to help to pinpoint the studies that unfairly influence the overall estimate of treatment effect.

Any missing data should be described in the Discussion at the end of the review. This demonstrates that the reviewers have considered the influence of the missing data on the results (149).

4.5.5 Assessment of heterogeneity

a) Definition of heterogeneity

In a meta-analysis, heterogeneity refers to the effects of the intervention displaying more variation than random effects (chance) would alone. It can be caused by many different factors, such as variation in participant characteristics, blinding or concealment of allocation methodology (which may also bring about a higher risk of bias), differences in how outcomes are measured or where there are many different interventions for the same condition of interest (148).

b) Determining levels of heterogeneity

For assessing the level of heterogeneity, I would look at the trials reporting the same outcomes that I could include in a meta-analysis.

Heterogeneity can be crudely evaluated by inspecting a forest plot for overlap of the CIs. If they have poor overlap, it suggests that there is heterogeneity. The chi-squared test is automatically shown on forest plots and provides more information about whether the heterogeneity is simply due to chance. This is coupled with a p-value. A low p-value and large chi-squared test implies variation of treatment effects beyond the realms of chance. It is important to note, however, that the chi-squared test has low power for a small

number of studies. In these cases, I would consider the p-value and appearance of CIs on the forest plot.

I also planned to use the I^2 statistic, which describes the percentage of variability due to heterogeneity rather than chance. A low percentage (up to 40%) implies low heterogeneity and a higher percentage (the levels are shown in the protocol, **Appendix 2**) suggests more substantial heterogeneity. However, the I^2 statistic should also be interpreted with caution. Again, I would judge this alongside the P value and the overall appearance of the CIs on the forest plot (148).

4.5.6 Assessment of reporting bias

To assess reporting bias, I would firstly compare the outcomes in the protocol of a study (where available) with the outcomes in the report. Otherwise, the methods section of a report could be compared with the results. These processes would highlight any areas that were selectively reported in the results in order to reflect a particular treatment effect.

Additional information could be requested from the study authors, although this is not always possible. I would search clinical trials registries for any unpublished data on a study and deal with missing data transparently, as described in section 4.5.4. I planned to examine the missing data very closely to determine whether certain results were deliberately left out, for example, if investigators only reported positive results of an intervention.

I also planned to consider sources of funding and conflicts of interests within the group of study investigators. These may influence the reporting of results and introduce publication bias (153).

a) Funnel plots

A funnel plot is a scatter plot that measures the effect estimate against the size of the study. There should be a positive correlation between the estimated intervention effect and the size of the study. Results from the smaller studies should scatter more widely at the bottom of the graph, giving the appearance of a funnel. If there is publication bias, the funnel plot will lose the symmetry of the inverted triangle shape (153).
If more than 10 studies were included in the review, I would construct a funnel plot to assess the risk of publication bias.

4.5.7 Data synthesis

I planned to use forest plots to display results graphically and assess heterogeneity.

a) Fixed effects and Random effects models

There are also two statistical models that are used for meta-analysis in the RevMan® software: the fixed effects model and random effect model. The fixed effects model assumes that all studies are measuring the one true treatment effect and that any differences between studies are simply due to random error (chance). The studies are assumed to have the same conditions and characteristics. If there were no random error, the results would be the same. In a fixed effects model, the CI is smaller than in a random effects model.

A random effects model assumes that the treatment effect varies between studies and allows for heterogeneity. The variance within studies and between studies is incorporated. Because of this, the CI is usually wider in a random effect model.
It is important to consider using each model, depending on the levels of heterogeneity (153).

b) Using the Fixed Effects and Random Effects models

I aimed to use the fixed effect model for low levels of heterogeneity (up to 40%). (As it assumes no heterogeneity, it is unrealistic to use for an I^2 of greater than 40%). I aimed to use a random effects model for heterogeneity greater than 40%. However, a summary from this model may not be accurate if there is high risk of bias, due to the relatively wide CI. Furthermore, a random effects model gives smaller studies greater weighting than a fixed effects model, which may influence the estimate of treatment effect. I would therefore compare both models to assess the influence of these studies on the overall effect of the intervention (153).

4.5.8 Subgroup analysis and investigation of heterogeneity

I planned to undertake a subgroup analysis if studies showed heterogeneity greater than 40% (154). Areas of subgroup analysis are described in the protocol in **Appendix 2.**

a) Sensitivity analysis

In the previous sections, I have described methods and tools that help reviewers come to decisions and overall findings based on these data. Sometimes, the results of a meta-

analysis can be based on findings that are not very accurate or reliable. Unit of analysis issues (e.g. using crossover trials), missing data, high risk of bias and inappropriate analysis methods can contribute to this. Therefore, it is recommended that reviewers undertake a sensitivity analysis at the end of a review to evaluate the robustness of their findings.

I planned to do this by excluding trials that have a high risk of bias or those with a crossover design in a second meta-analysis, to look for any change in the estimate of treatment effect (148).

4.5.9 Summary of Findings table

At the conclusion of a Cochrane review, it is recommended that reviewers summarise the findings for the outcomes outlined in their protocol. Systematic reviews of interventions are usually long and complex, with discussion about the many different factors affecting results. It can therefore be confusing for the reader to understand clinically significant risks and benefits of the intervention. The Summary of Findings (SoF) table is designed to present this information clearly (129).

I aimed to include the measures for each of our outcomes **(see protocol, Appendix 2)** for the interventions described the studies e.g. laxative agents, control or other therapies. If an outcome is not reported, I would specify this in the table with the description, "data not reported". For each outcome, I would state the number of participants and studies, the comparative risk of the intervention and control and the relative effect (RR or MD). For each outcome I aimed to use to the Grading of Recommendations, Assessment,

Development and Evaluation Tool (GRADE) to assess the quality of evidence (high, moderate, low or very low) (155).

4.6 Summary

In the previous sections, I explained the methods used to generate the review, "Interventions for the prevention of DIOS in cystic fibrosis". To do this, I clarified the eligibility criteria for inclusion of studies and explained the process of searching for studies using medical databases and registries. I then went onto to describe the process of data collection and data extraction, in which I gathered detailed information from the included studies. Next, I outlined the strategies for 10 main areas of data analysis, and explained the importance of each method. These main areas were: The assessment of bias in studies, measuring treatment effects, unit of analysis issues, dealing with missing data, assessment of heterogeneity, assessment of reporting bias, data synthesis, subgroup analysis, sensitivity analysis and summary of findings table.

In the next section, I will present the results from data extraction and analysis. These will be described using a combination of text and figures. I will then discuss the importance and significance of the main findings.

4.7 Results

4.7.1 Description of studies

a) Results of the search

Of the 2631 studies (after 588 duplicates were removed) identified by initial searches, I found 8 potentially eligible studies for inclusion. Of these, 1 study was included and 7 were excluded. The study flow diagram was based on the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (156) and was produced on RevMan®. It is shown below in Figure 4.3.

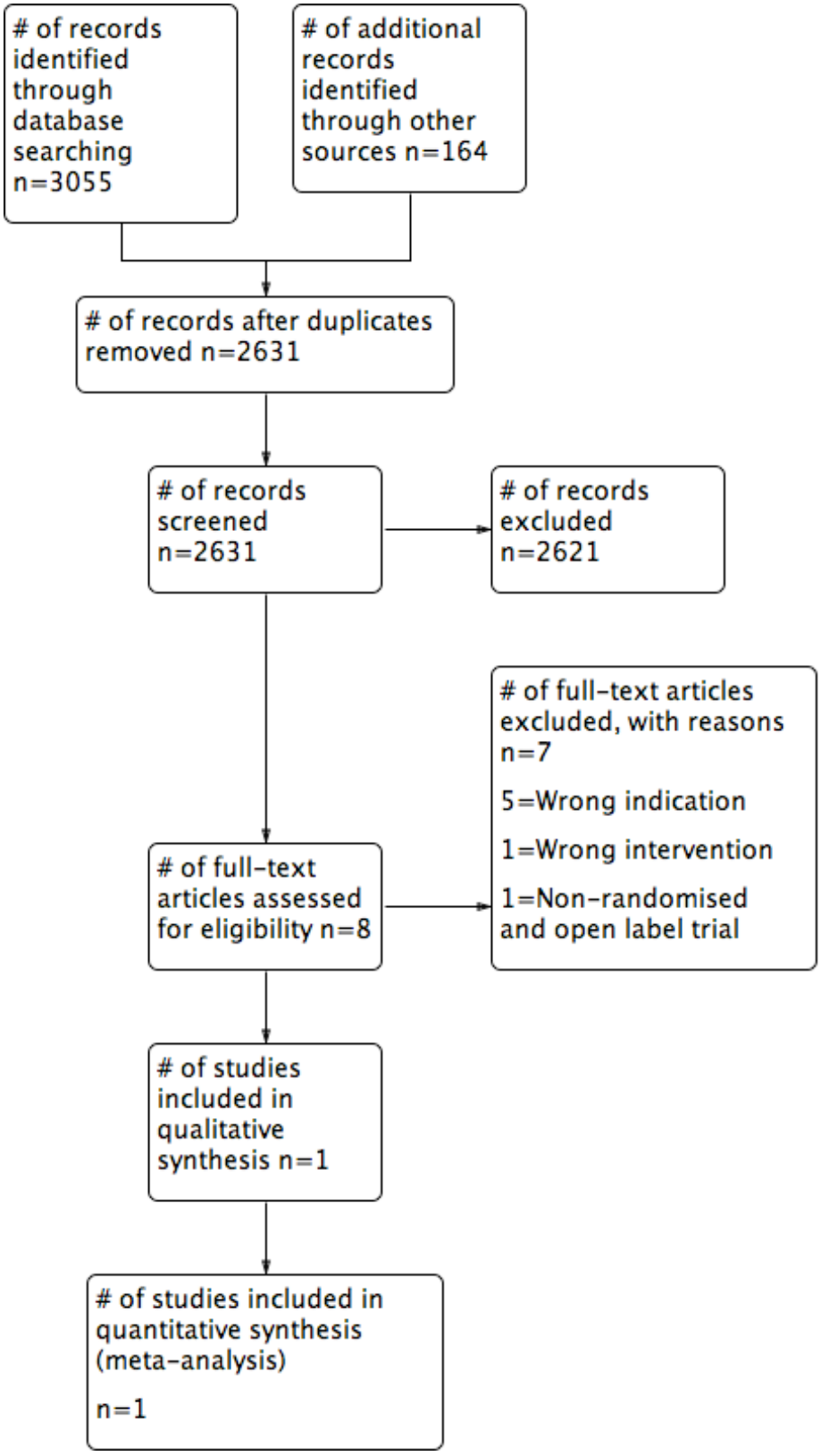


Figure 4.3: Study flow diagram for the review, “Interventions for the prevention of DIOS”

b) Included studies

The included study (n=17) was available as an abstract and full text (157).

c) Trial characteristics

The study was a randomised, double-blind, placebo-controlled crossover trial. It was based at a single centre in Toronto, Canada.

The duration of the trial was 12 months. The participants were randomised into two groups to take either the placebo or active drug and then swapped to the opposite group after 6 months. The potential carry-over effect of the drug was also accounted for (see section 4.1.5) (157).

d) Participant characteristics

The number of participants was 17. The trial did not specify the recruiting age, but decided to recruit both male and female participants. The mean age (years) and range for the age of participants in the trial was 21.0 (12.9 to 34.9) and there were 5 female and 12 male participants.

In terms of the inclusion criteria, the trial required participants to have a diagnosis of CF and to have had one or more episodes of DIOS in preceding 12 months.

The trial excluded pregnant participants, those with current gastrointestinal obstruction and with serious cardiovascular, neurological, renal or hepatic disease. Participants with other causes of abdominal pain e.g. peptic ulcer disease and inflammatory bowel disease were also excluded, as were those who regularly used metoclopramide, domperidone or an anticholinergic drug.

The baseline characteristics for participants were stated; there were no significant differences in the clinical characteristics between them (157).

e) Intervention

As the trial had a crossover design, participants served as their own controls.

The active drug was cisapride. Participants were randomised into two groups and received (in a blind fashion) placebo or cisapride for 6 months each. They then switched to the other treatment arm for the second 6 months of the study. Patients between 40 and 50kg received 7.5mg of either placebo or cisapride 3 times per day and patients above 50kg received 10mg of either placebo or cisapride 3 times per day.

The trial accounted for any potential carry-over treatment effect of the active drug. The investigators did this by analysing the data in two ways. Measurements were recorded twice for each 6-month period: once every 3 months. Firstly, investigators took an average of the two measurements. They then discarded the measurements from the first 3 months, to account for any cumulative effect of the drug (157).

f) Outcome measures

The radiological diagnosis of DIOS was measured in the trial using supine abdominal radiographs. Patients were interviewed for adverse effects and also reported any gastrointestinal and global symptoms, with the use of scoring systems. Other outcomes included the number of participants requiring therapy for DIOS and stool weight.

Irrelevant outcomes for our review included: Anthropometric measurements (e.g. mid-arm circumference, skin fold thickness), frequency of pulmonary infections, pulmonary

function (%FEV1), nutritional/calorie intake, routine laboratory tests (e.g. urinalysis, complete blood count) and number of hospital admissions.

g) Excluded studies

I excluded 7 studies for various reasons. 5 trials were excluded because the active drug was used for the wrong indication and therefore the trials had irrelevant outcomes. In 4 of these, N-acetylcysteine was used as a mucolytic for lung disease in CF, rather than for the prevention of DIOS (158, 159, 160, 161). In the other, N-acetylcysteine was used to improve malabsorption in CF rather than for the prevention of DIOS (162).

Another study was excluded because the intervention was for the treatment of DIOS, rather than the prevention of DIOS (163). The other study was excluded because it was open-label (i.e. no blinding of participants and personnel) and the participants were non-randomised. The risk of bias was too high for this study to be reliable (164).

4.7.2 Risk of bias in included studies

I constructed a risk of bias summary for this review using RevMan®, which is shown below in Figure 4.4.

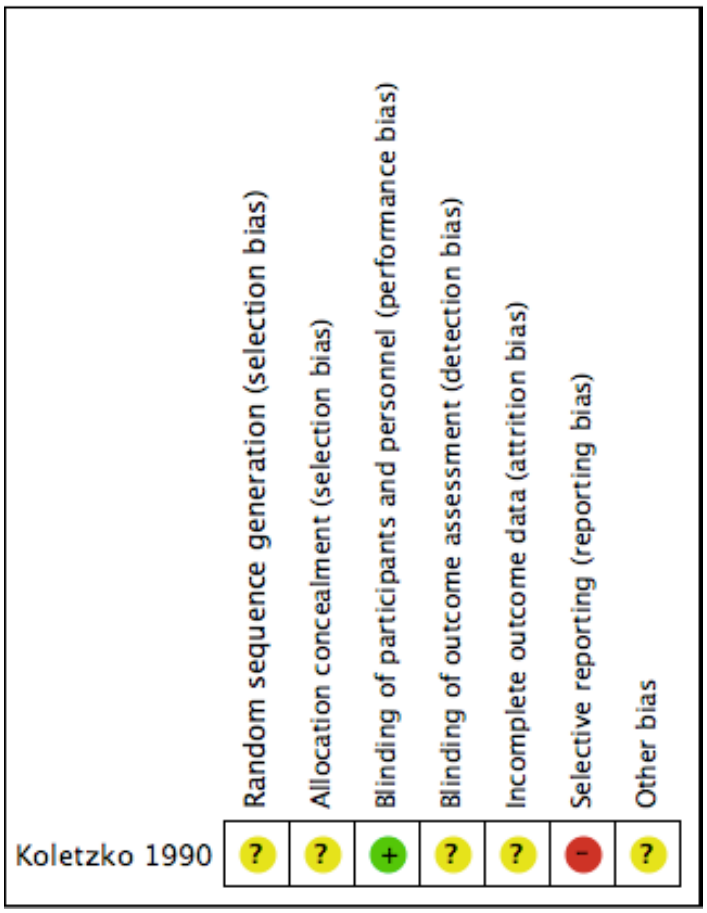


Figure 4.4: Risk of bias summary for the included study (140) in this review.

a) Allocation

The trial stated that participants were randomly allocated to start with either cisapride or placebo, but it did not specify how the sequence was generated or the method used for concealment of allocation (140). I therefore ranked the study as having an unclear risk of bias for these categories. WC and I initially disagreed on the ranking for this domain; he thought it should have a low risk of bias because the study authors had stated that participants were “randomly allocated”. However, I argued that we could not know how the participants were randomly allocated; truly random methods may well have been used (such as a random computer generator) but the participants could have been quasi-randomised, (such as allocation of clinic days). Therefore, because the study authors did

not specify how exactly participants were randomised, we ultimately agreed that there was an unclear risk of bias for this domain.

b) Blinding

Participants and personnel were blinded and the placebo was identical in taste and appearance to cisapride (140). For this category, I ranked the trial as having a low risk of bias.

For the blinding of outcome assessors, the overall risk of bias was unclear. Only three outcomes stated that the investigators were blinded. The first of these was gastrointestinal symptom scores, where the blinded patients acted as their own assessors. Second was for the assessment of supine abdominal radiographs, where a paediatric radiologist judged these in a blind fashion. Third was for the assessment of nutritional intake and stool collection, where the blinded patients recorded their own intake and investigators also worked in a blind fashion. For the other outcomes, the risk of bias was unclear. Although blinded patients scored their own global symptoms, physicians assessed them too and I could not make the assumption that the physicians were blinded. There was no mention of blinding for the other outcomes in the study: anthropometric measurements, number of hospital admissions, pulmonary function and frequency of pulmonary infections, laboratory tests, abdominal circumference and intestinal lavage therapy. This was another area of disagreement between WC and myself. WC sensibly pointed out that the blinding of outcome assessors would not make much difference for certain outcomes that were very objective in nature, such as anthropometric measurements, number of hospital admissions, laboratory tests and pulmonary function testing. However, the assessment of global symptoms was a more

subjective outcome and one in which blinding of outcome assessors would be important. Therefore, as there was no mention of blinding for this, we agreed to rank this domain as having an unclear risk of bias.

c) Incomplete outcome data

For gastrointestinal symptom scores, global symptom scores and intestinal lavage therapy, there was no missing data. For nutritional intake and stool losses, only 10 out of 17 participants were represented in the results. This was because 3 participants had refused to perform quantitative food intake protocols and stool collections and 4 participants were excluded due to incomplete or inaccurate food records or stool collections. Although the investigators gave reasons for the missing data, there was no mention of an ITT analysis. For anthropometric measurements, adverse effects, pulmonary function, frequency of pulmonary exacerbations, number of hospital admissions, radiological signs of DIOS and laboratory values, there was insufficient information to judge whether there was missing outcome data (140). For these reasons, I ranked this category as having an unclear risk of bias.

d) Selective reporting

I did not have access to the protocol, so could not compare the list of outcomes in the protocol with the results reported in the study. However, I compared the outcomes listed in the Methods section with the outcomes reported in the Results section.

The investigators stated that they would calculate the difference in weight and percentage of ideal weight for height during the two periods, using t tests for comparison. However, these changes and results of t tests were not reported in the results. Pulmonary

function testing and radiological findings were measured at baseline and after 6 months, but the results were unreported. Anthropometric measurements (e.g. mid-arm circumference and skin fold thickness), physical examination findings, number of hospital admissions and frequency of pulmonary infections were measured every 3 months but insufficiently reported. Laboratory test results (blood and urine analysis) were also measured but not reported (140).

Due to multiple incidences of selective reporting, I ranked the study as having a high risk of bias for this category.

e) Other potential sources of bias

There was insufficient information to judge whether there was a risk of bias from other sources. In terms of publication bias, the pharmaceutical company, "Janssen Pharmaceutica Incorporated", supported the trial, but there was no evidence to suggest that they had any part in sponsorship or funding. There was also no indication to suggest conflicts of interest from the authors, but this was not explicitly stated (140). Therefore, I could not assume that the risk of bias was low.

Due to insufficient information regarding other sources of bias in the study, I decided to rate this category as having an unclear risk of bias.

4.7.3 Effects of interventions

In this section, I will compare the main outcomes from our protocol with the outcomes in the included trial.

a) Summary of Findings table

Please see **Appendix 3** for the Summary of Findings table for oral cisapride versus placebo.

b) Oral cisapride versus placebo

Oral cisapride versus placebo was the only comparison used in the included trial (140). No other active drugs were assessed.

i) Primary outcomes

1. **Complete or incomplete DIOS diagnosed either clinically (e.g. abdominal masses, or distension or pain) or radiologically (e.g. dilated bowel or faecal mass).**

The radiological diagnosis of DIOS was an outcome measure for this trial. It was measured using a scoring system for the total radiological severity and severity of each criterion (e.g. degree and distribution of faecal retention, presence of bubbly granularity in the right iliac fossa, degree of small bowel dilatation and nodularity of the intestinal mucosa). However, the numerical data was not reported in the results. The investigators stated that there was no significant difference between cisapride and placebo (140).

2. **Adverse effects from treatments**

    i. Serious adverse effects of treatment regimens (including, but not limited to, rectal bleeding, intestinal perforation, mucosal erosions, anaphylactic reaction, vomiting with electrolyte disturbance)

    ii. Other adverse effects of treatment (e.g. diarrhoea or soiling, abdominal distension, loss of continence or pain)

Participants were interviewed for adverse effects every 3 months. The trial reported that no adverse effects were noted (140).

ii) Secondary outcomes

1. **Time to hospital admission**

    i. All causes

    ii. Due to DIOS

This outcome was not assessed or reported in the trial (140).

2. **Patient-reported quality of life (QoL) scores**

This outcome was not assessed or reported in the trial (140).

3. **Patient-reported symptom scores**

Two different symptom scores were assessed and reported by participants in this trial: gastrointestinal symptoms and global symptoms.

For gastrointestinal symptoms, a lower score signified a better score. Participants scored the severity and frequency of 10 different gastrointestinal symptoms and total gastrointestinal symptoms at 3 monthly intervals. The trial reported results for a 6-month period, where the scores ranged from 2-20 for individual symptoms and 20-100 for the total gastrointestinal symptom score (140).

As the data came from a crossover trial where individuals acted as their own controls, the number of participants for each group was automatically doubled in RevMan®. Due to the

way the data were presented, I needed to calculate the mean difference and standard error in order to analyse the average symptom score using the generic inverse variance (GIV). I used the fixed effects model because there was a single study in the review, so there would be no heterogeneity (I planned to use the fixed effects model for an I^2 value below 40% and use a random effects model for an I^2 value of above 40%). The results favoured cisapride over the placebo. The total gastrointestinal symptom score was statistically significant at 6 months with an MD of -7.60 (95% CI -14.73 to -0.47) using the fixed effects model. Individual symptom scores of interest were abdominal distension and abdominal pain, as they related to the symptoms of DIOS.

There was no significant difference between cisapride and placebo for abdominal distension or abdominal pain at 6 months. Abdominal distension showed a MD of -0.90 (95% CI -2.39 to 0.59) and abdominal pain showed a MD of -0.4 (95% CI -2.05 to 1.25).

The figures below are screenshots from the RevMan® software (131). They show the statistical analysis for the relevant gastrointestinal symptom scores, including the total gastrointestinal score and the scores for abdominal distension and for abdominal pain.

Figure 4.5: Statistical analysis for patient-reported total gastrointestinal symptom scores for cisapride versus placebo.

Comparison: 2 Cisapride versus placebo, Outcome: 2.13 Total gastrointestinal symptoms

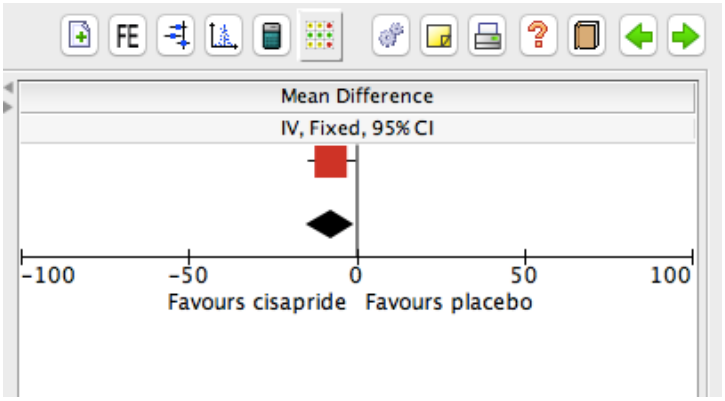
Study or Subgroup	Mean Differenc	SE	Cisaprid Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Koletzko 1990	-7.6	3.6401	17	17	100.0%	-7.60 [-14.73, -0.47]
Total (95% CI)			17	17	100.0%	-7.60 [-14.73, -0.47]

Heterogeneity: Not applicable

Test for overall effect: Z = 2.09 (P = 0.04)

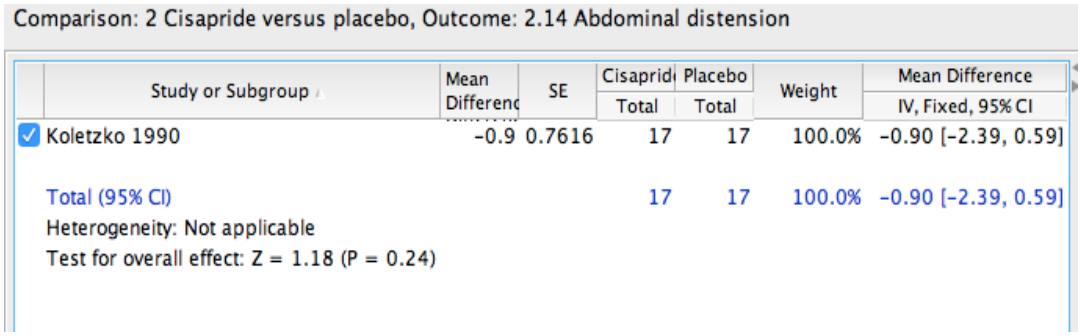
There is no I^2 value because there is no heterogeneity, as there is only one study (The definition of I^2 can be found in section 4.5.5). The weight of the study is 100% because there are no other studies in the review. The p value is statistically significant (<0.05) and so it rejects the null hypothesis (that there is no difference between cisapride and placebo). The confidence interval does not include 1, which also reflects a significant result.

Figure 4.6: Forest plot for patient-reported total gastrointestinal symptom scores for cisapride versus placebo.



The significance of the p value is supported by the black diamond (the pooled results) not overlapping with the line of no effect.

Figure 4.7: Statistical analysis for patient-reported abdominal distension symptom scores for cisapride versus placebo.



Comparison: 2 Cisapride versus placebo, Outcome: 2.14 Abdominal distension

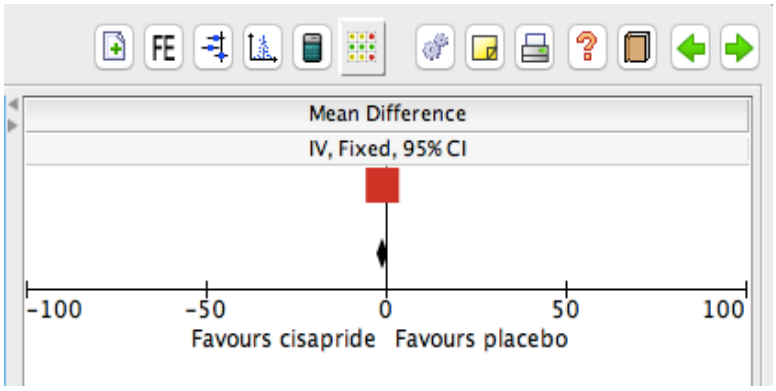
Study or Subgroup	Mean Differenc	SE	Cisaprid Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Koletzko 1990	-0.9	0.7616	17	17	100.0%	-0.90 [-2.39, 0.59]
Total (95% CI)			17	17	100.0%	-0.90 [-2.39, 0.59]

Heterogeneity: Not applicable

Test for overall effect: Z = 1.18 (P = 0.24)

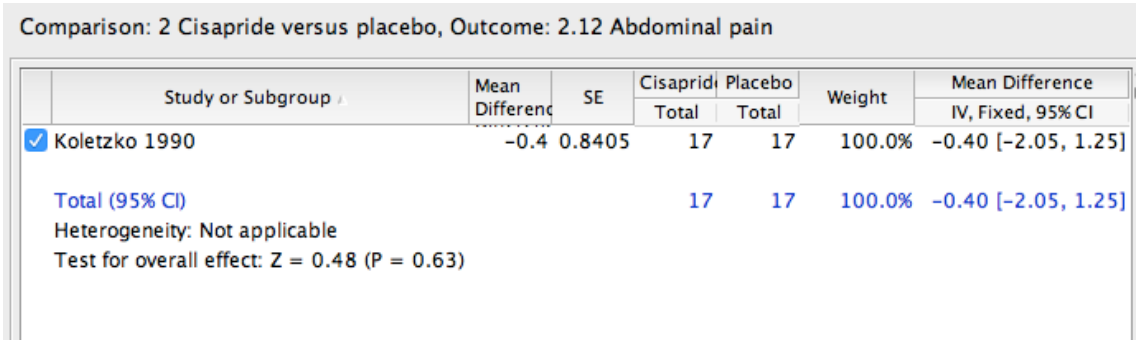
Here, the p value is not statistically significant, which implies that there is no difference between cisapride and placebo.

Figure 4.8: Forest plot for patient-reported abdominal distension symptom scores for cisapride versus placebo.



The pooled result is now touching the line of no effect, which reflects the non-significant p value.

Figure 4.9: Statistical analysis for the patient-reported abdominal pain symptom scores for cisapride versus placebo.



Comparison: 2 Cisapride versus placebo, Outcome: 2.12 Abdominal pain

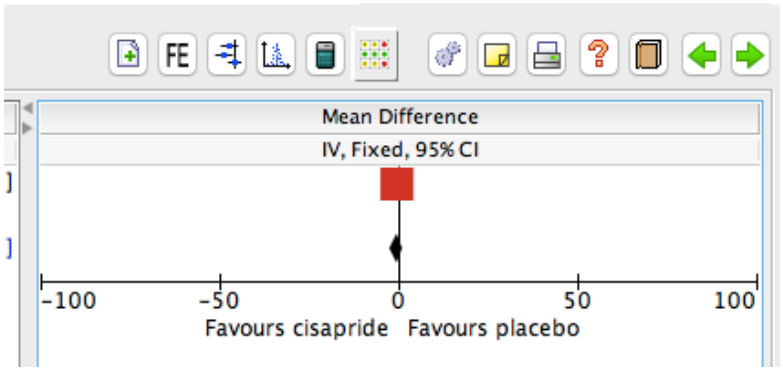
Study or Subgroup	Mean Differenc	SE	Cisaprid Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Koletzko 1990	-0.4	0.8405	17	17	100.0%	-0.40 [-2.05, 1.25]
Total (95% CI)			17	17	100.0%	-0.40 [-2.05, 1.25]

Heterogeneity: Not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

Again, the p value shows no statistical significance between cisapride and placebo.

Figure 4.10: Forest plot for patient-reported abdominal pain symptom scores for cisapride versus placebo.



The black diamond is touching the line of no effect, which supports the p value of a non-significant result.

The precision of the results is discussed later in this chapter.

Participants also recorded global symptom scores at the end of each 6-month period (i.e. after the full course of either cisapride or placebo). The data was reported as the number of participants who fell into 3 categories: those who felt better, the same or worse with the treatment (140). Due to the way in which the data was reported, I was unable to measure this outcome as continuous or dichotomous. On advice from the CRG, I presented the data in a simple table on RevMan® (131) to show the numbers of participants for each category. The study reported that the results favoured cisapride and were statistically significant ($p<0.05$).

I have taken a screenshot of the table, shown below in Figure 4.9:

Figure 4.11: Alterations in patient-reported global symptom scores with cisapride and placebo.

⊟ 1 Alterations in global symptoms

Intervention	Total number of participants	Felt better	Felt the same	Felt worse
Cisapride	17	12	2	3
Placebo	17	3	2	12

4. **Tolerability (participant- or investigator-reported rates of concordance)**

This outcome was not assessed or reported in the trial (140).

4.8 Discussion

4.8.1 Main findings

There was only one included study in this review that compared cisapride to placebo for the prevention of DIOS. The results found that cisapride improved the total gastrointestinal symptoms for patients during the study period. Patients generally felt better taking cisapride and those with worse symptom scores benefitted most from the drug. There were also no side effects noted from cisapride. There were no significant differences between cisapride and placebo for radiological diagnosis of DIOS and individual symptom scores that were relevant to the review, such as abdominal distension and abdominal pain. The findings of the review were limited and demonstrated that overall, there is a huge lack of evidence for the prevention of DIOS in CF.

4.8.2 Overall completeness, relevance and applicability of the evidence

My objective was to compare various laxative agents for the prevention of DIOS in children and adults with CF. As there was only one comparison in the review (cisapride versus placebo), I could not perform a meta-analysis of the data. Hence, I was unable compare the relative efficacies, safety and adverse effects of different laxative agents as I had intended. The following sections detail that the evidence for the prevention of DIOS is only based on one low quality study (see section 4.8.3) that was conducted nearly 30 years ago with a drug that can no longer be prescribed in the UK; therefore, the findings are incomplete, irrelevant and largely inapplicable.

a.) Outcome measures

I was unable to report several important outcome measures that I had set out in the protocol. My primary outcome was to measure the diagnosis of complete or incomplete DIOS (diagnosed either clinically or radiologically). In the trial, the radiological diagnosis of DIOS was measured and the investigators reported a non-significant difference between cisapride and placebo. However, the trial results were not fully reported so I could not analyse the data.

The measure of adverse effects from treatments was another primary outcome. The trial stated that there were no adverse effects from treatments, but did not expand on this.

The trial also failed to assess nearly all of my secondary outcomes. The unreported outcomes were: time to hospital admission, patient-reported quality of life scores and tolerability. The number of hospital admissions was described as an outcome in the trial, but I judged it to be irrelevant, as it was not reported as time-to-event data and did not specify the reason for each hospital admission.

However, the trial managed to assess and report one of my secondary outcomes: the patient reported symptom scores. There were two types of symptom scores used in the trial: gastrointestinal symptom scores and global symptom scores. There is reliable evidence to support the use of patient reported outcome measures (PROMs) in healthcare. A 2013 systematic review demonstrated that effective PROMs improve patient-provider communication, patient satisfaction, the monitoring of treatment response and the detection of unrecognised problems (165). These findings could therefore be applicable to clinical practice.

b.) Participants

They participants were relevant to the review because all had a diagnosis of CF and included both children and adults. However, the population size was very small, which limited the precision of the effect estimates (see section 4.8.3iv). In addition, the age range only included older children and young adults. There were no findings to demonstrate the safety and efficacy of cisapride in CF patients of other age ranges. There were also 12 male participants compared to only 5 female participants, which could have unfairly affected the results. In 2016, Munck found that female gender was associated with recurrent DIOS (75% vs. 52%, p = 0.04) (111). If this is the case, the results for the radiological diagnosis of DIOS may not be accurate, since the data mostly represents male participants.

c.) Intervention

The study intervention was cisapride. Cisapride is not categorised as a laxative agent, so it is debatable whether it meets the criteria for “types of interventions” according to the protocol. It is typically used a gastro-prokinetic agent. I could argue that cisapride functioned as a laxative agent in the trial and so should therefore be accepted. However, cisapride has since been withdrawn from the UK market due to its cardiac side effects (see section 4.8.5 for more detail). Therefore, the drug has no applicability in clinical practice unless it can be re-approved for licence.

4.8.3 Quality of the evidence

a.) Strengths

There were some methodological strengths of the included study. The design of a crossover trial meant that participants acted as their own controls, which eliminated clinical differences between the two treatment arms. The investigators also considered and eliminated the potential carry-over treatment effect that could occur with this study design. As the trial had also measured the mean and standard deviation for the active drug and placebo, I was also able to carry out a paired analysis using the generic inverse variance method in RevMan® (131). This is more accurate at estimating a treatment effect than an unpaired analysis, as it makes comparisons between the same subjects, hence taking advantage of the crossover design (151).

Certain domains of the Risk of Bias Tool demonstrated a high quality study design, such as the blinding of participants and personnel. Some outcomes also reported blinding of the assessors e.g. supine abdominal radiography.

b.) Weaknesses

The review demonstrated far more examples of low quality evidence, as based on the GRADE criteria (166). The Summary of Findings table in **Appendix 3** illustrates this. First and foremost, there was only one included study that had a small number of participants. The trial was also conducted almost 30 years ago, so its results have limited relevance today.

Having a single study review meant that I could not perform the meta-analysis methodology. Hence, I was unable to assess for heterogeneity, construct funnel plot for assessment of reporting bias, perform a subgroup analysis (this would only be done if results showed >40% heterogeneity), use the random effects model (this would only be

compared against the fixed effects model if results showed >40% heterogeneity) or undertake a sensitivity analysis. A lack of meta-analysis meant that I was unable to fully evaluate the robustness of the review's findings, or comment on the consistency of the results.

i) Risk of Bias

For the outcomes in the Summary of findings table **(Appendix 3)**, I downgraded them in quality for unclear methods in sequence generation and allocation concealment, as the investigators stated that the participants were randomised but did not specify how. There was also risk of selective reporting for the radiological diagnosis of DIOS, as the investigators did not fully report the results.

In addition to the outcomes in the Summary of Findings table, there were missing data for the outcomes measuring nutritional intake and stool losses, for which the trial reported results from 10 participants rather than 17. The trial gave reasons for the missing data and I judged that it was missing at random, but the investigators did not (to my knowledge) conduct an ITT analysis.

The trial was found to have a high risk of bias for selective reporting for other outcomes in addition the radiological diagnosis of DIOS. On multiple occasions, the authors explained how they would measure an outcome in the Methods, but failed to fully report the findings in the Results. They briefly mentioned some findings e.g. "pulmonary function testing revealed no differences between the placebo and cisapride periods" but did not report the data. I could not find a valid reason for why the investigators fully reported some results but not others. Consequently, there was a high risk of selective reporting bias across the whole study.

The included study revealed an unclear risk of bias across most of the domains. This was because the report did not provide sufficient information required for the risk of bias assessment. The most prominent areas of unclear bias were: random sequence generation, allocation concealment and incomplete outcome data.

ii) Inconsistency

There was no heterogeneity as there was just one included study. Therefore, I could not downgrade the quality of the findings for this category.

iii) Indirectness

Due to the intervention used in the study, there was a great deal of indirectness shown in the review. Firstly, cisapride is not a typical laxative agent and so does not meet the specific objectives of investigating "different laxative agents" for the review. Secondly, the study was conducted in 1990 when cisapride still prescribed in the UK. Since then, it has been removed from the market due to rare but serious cardiac effects (see section 4.8.5) and is no longer permitted for use. These issues led me to downgrade the evidence two levels for the directness of the review.

iv) Imprecision

Although the confidence intervals for the outcomes in the Summary of Findings table did not appear to be wide according to the forest plots, I downgraded the evidence one level for precision due to the small number of participants. When the sample size is small, there is less information about the treatment effect, resulting in more uncertainty and hence, less precision.

v) Publication bias

I was unable to produce funnel plot to test for publication bias because there was only one study in the review. I could not assume that one study meant that there was no risk, but equally I did not strongly suspect publication bias. I therefore rated publication bias as "undetected" in the Summary of Findings table.

4.8.4 Potential biases in the review process

a) Strengths

During the process of study screening, data collection and extraction, there was a low risk of bias. WC and I independently screened the studies and so that we could come to our own conclusions. Afterwards, we worked out disputes mainly by discussion, but FG acted as an external arbiter to resolve some disagreements, namely on ranking domains of bias. I also endeavoured to be very thorough as I collected the data. I did this by collecting it in two ways. I firstly completed the data collection form given to us by the CRG, which provided a good foundation for each important area e.g. participants, interventions, outcomes. Secondly, I used the more detailed data extraction form on Covidence© to obtain any other important information. I also completed the risk of bias assessment on Covidence©.

For the searching of studies, the risk of bias was very low. NH (a Cochrane information specialist) assisted me in developing a comprehensive strategy to ensure that all relevant trials were obtained. I ran each search twice and checked that the number of results was the same for each (i.e. to account for typing errors).

None of the authors for the review (myself, WC and FG) had any conflicts of interest to declare.

b) Weaknesses

i) Differences between protocol and review

Potential risks of bias in the review process included some differences between the protocol and review. I stated that the review would compare different laxative agents for the prevention of DIOS, but the included study assessed the efficacy and safety of cisapride, which is not classed as a laxative agent. In hindsight, I should have mentioned that other agents could sometimes be used to prevent DIOS. This would have improved the transparency of the Methods and prevented the potential risk of bias. However, it was a team decision to include the study in the review and in all other aspects (e.g. the types of participants, indication and study design), I believed it to meet the inclusion criteria. The lack of evidence on the review topic may have also motivated me to look further afield for other interventions used for the prevention of DIOS.

ii) Unsuitable trials

The motivation to perform a meta-analysis led me to be overly optimistic in the assessment of one particular trial (164). Originally, I intended to include this trial in the review and completed the process of data extraction for it. However, after corresponding with the CRG, I later removed it for having a high risk of bias in multiple domains. The trial had a non-randomised, open label design and was therefore not suitable for inclusion.

iii) Additional outcomes

Although our outcomes were pre-specified in the protocol for the review, there were some outcomes from the included study that I thought were clinically relevant to the review question. Initially, I wished to include these additional outcomes. The first was stool weight. Stool weight is a relevant outcome because it illustrates the quantity and relative ease of bowel movements in participants. Lower stool weight suggests smaller, harder stools that can cause faecal impaction and therefore bowel obstruction; higher stool weight means participants are passing a substantial quantity of stool, suggesting normal bowel movements with no obstruction. This outcome correlates with the efficacy of the intervention.

The second outcome I considered to be clinically relevant was the number of patients requiring intestinal lavage therapy for DIOS during the study period. I considered this to be applicable because it would demonstrate differences in efficacy between the active drug and placebo. That is, the higher the number of participants requiring lavage during the study period, the less effective the intervention in preventing DIOS. Furthermore, this outcome would highlight the safety of the intervention. Patients who require immediate treatment for DIOS may be at risk of developing complete bowel obstruction, so if participants taking the active drug required immediate treatment or invasive therapy during the study period, it may raise concerns about the safety of the study drug.

However, after communicating with the NJ and FG, I came to the conclusion that the inclusion of these additional outcomes would strongly indicate reporting bias. Although I considered these outcomes to be clinically relevant, they were not identified at protocol stage by any of the clinical experts or brought to our attention in the peer review

comments. It could appear that I was adapting the review to suit the study outcomes, rather than basing the review on the rationale of the original clinical question.

4.8.5 Agreements and disagreements with other studies or reviews

The included trial was published in 1990 when cisapride was a fully licenced drug in the UK. It was commonly used to treat gastric and digestive disorders in children and adults. However in July 2000, the Medicines Control Agency suspended the use of cisapride in the UK due to the rare but serious cardiac effects associated with the drug. These effects were associated with ventricular arrhythmias and in some cases, sudden death. Between 1988 and 2000, the UK received reports of 60 adverse cardiovascular reactions of the drug, 5 of which resulted in death. Worldwide, there were 125 fatal reactions to cisapride, which led to many other countries suspending the marketing for the drug e.g. USA, Canada and Germany (167).

4.9 Summary

In this chapter, I have presented the methods, results and discussed the main findings for the Cochrane Review: "Interventions for preventing DIOS in CF". The most significant outcome from this review was that there is a severe lack of evidence for the prevention DIOS in CF. After carefully constructing the eligibility criteria and outcomes for the review, and running extensive searches on medical databases and registries, it was very discouraging to find that there was a single study for inclusion. Furthermore, this study failed to address any of my primary outcomes. It also had an unclear risk of bias for most domains and was very poor in quality. But most importantly, the study drug (cisapride)

can no longer be prescribed in the UK, which renders any findings irrelevant for current clinical practice.

In the next chapter, I will present and discuss the findings from the review on, “Interventions for the treatment of DIOS”. In chapter 6, I will present and discuss the findings from a nationwide survey about the current management of constipation and DIOS. In chapter 7, I will draw my conclusions from all the main findings of this thesis (the two Cochrane reviews and the survey). From there, I will propose implications for future clinical practice and research.

Chapter 5: Cochrane Systematic Review for Interventions for the treatment of DIOS in CF.

5.1 Objective

- To assess the effectiveness and safety of different groups of laxative agents for treating distal intestinal obstruction syndrome (incomplete and complete) in children and adults with CF.

5.2 Writing the Protocol

Before the academic year started, FG drafted the protocol and after attending the first part of Cochrane training, I added content and references to the background section (the introduction, description of the condition and description of the intervention). For the section, “description of the intervention”, I grouped and defined the different types of laxative and specified the comparisons between laxative agents (e.g. osmotic laxative versus stimulant laxatives). I also drafted the section on “types of outcome measures”. I also made amendments to the section entitled “electronic searches” with the help of a Cochrane information specialist, NH.

As I was not able to design the protocol for my own review, I decided to involve myself in the development of the protocol for the prospective MPhil student. This was beneficial because it completed my "Cochrane experience".

I submitted the protocol on 27/02/2017 and it was sent back with peer review comments on 20/06/2017. I responded to the peer review comments and edited the protocol accordingly. As we are awaiting approval, the protocol is not yet published and I could therefore not include it in the Appendices of this thesis.

5.3 Eligibility criteria

Although the nature of the intervention for this review was different to that of the previous review (treatment versus prevention of DIOS), many areas of the PICOS criteria were the same for both reviews, such as the types of participants, types of studies and largely, the types of interventions. Therefore in the sections below, I will regularly refer back to the PICOS criteria of the previous review as described in Chapter 4.

a) Participants

I searched for studies including children and adults with CF (with all stages and severity of lung disease and with or without pancreatic sufficiency) (See Chapter 4 for more detail).

b) Intervention and Comparison

i) Types of interventions

Laxatives form the basis of the medical management of DIOS, whether that is prevention or treatment of DIOS. In this case, I wanted to assess laxatives for the treatment of acute incomplete or complete bowel obstruction.

In addition, I included surgery as a type of intervention for this review. Although seen as last resort, surgery is nevertheless a treatment for complete DIOS in cases where medical management has failed.

ii) Categorising the difference types of laxative

As with the previous Cochrane review, I decided to group the laxatives according to their mode of actions: osmotic laxatives, stimulant laxatives and mucolytics.

In DIOS, osmotic laxatives may soften the viscid stool (caused by the combination of mucus and faeces) that has accumulated in the bowel.

Stimulant laxatives are effective are stimulating peristalsis (104), so could reduce gut transit time and flush the mucofaeculant material that has adhered to the bowel wall. As depicted in the name, Mucolytics work by disintegrating the mucus produced in CF. They could therefore breakdown existing mucofaeculant material.

Please see Chapter 4 for more detail on the grouping of laxatives.

iii) Types of comparisons

I decided to compare various laxative therapies at any dose to placebo, no treatment or alternative laxatives for the treatment of DIOS.

c) Outcomes

As this review was assessing laxatives for treatment of DIOS rather than for the prevention of DIOS, the outcomes had to be specific to this objective and were therefore different.

Primary outcomes:

I aimed to assess the following primary outcomes for the review, "Interventions for the treatment of DIOS":

1. Time taken from start of treatment until the resolution of DIOS (diagnosed clinically or radiologically)
2. Treatment failure rate (e.g. clinician-determined need to change medical regimen or need for surgical intervention)

The first primary outcome for this review is useful for measuring the effectiveness of various laxatives for the treatment of DIOS. This type of outcome is commonly known in statistics as "time-to-event" data. However, the event i.e. resolution of DIOS, may not occur for various reasons. Some participants could be lost in the follow-up process, or suffer from a serious adverse effect that may worsen their condition (133).

There are various ways of assessing time-to-event data. The resolution of DIOS could be measured by allocating an agreed period of time in which the patient should be successfully treated. When that period of time ends, the participants who do not have resolution of DIOS could fall into the "treatment failure" category, the other primary outcome for the review. However in this case, we did not relate "treatment failure rate" to a period of time. Instead, "treatment failure" would be assigned to those participants who required a different medical regimen or surgical intervention, according to the expert opinion of a clinician.

Secondary outcomes:

I aimed to assess the following secondary outcomes for the review, "Interventions for the treatment of DIOS":

1. Recurrence rate of DIOS (diagnosed clinically or radiologically) after successful treatment

2. Adverse effects

    i) Serious adverse effects of treatment regimens (including but not limited to rectal bleeding, intestinal perforation, mucosal erosions, anaphylactic reaction, vomiting with electrolyte disturbance)

    ii) Other adverse effects of treatment (e.g. abdominal distension, soiling, loss of continence or pain)

3. Adherence

1. It is widely recognised that patients who have had a previous diagnosis of DIOS are more likely to be diagnosed with it again, compared to patients who have never had DIOS. I thought it would be useful to ascertain the exact figures of this by using study data of patients who were successfully treated for DIOS, hence why it is listed as the first secondary outcome for the review.

2. Adverse effects are listed in this review as a secondary outcome rather than a primary outcome. One of the primary outcomes of this review, "treatment failure rate" may already address some of the potential, adverse effects of a treatment. This is because the

treatment may have to be altered in cases where the patient finds it intolerable or has a serious adverse reaction. Adverse effects are also listed as a secondary outcome due to the nature of the intervention. For the prevention of DIOS, patients would most likely receive laxative treatment over a long period of time, in which adverse effects would have a more significant impact on the patient. Conversely, the treatment of DIOS involves a short course of laxative(s), so it is likely that adverse effects will have a lesser impact on the patient (obviously depending on the nature of the adverse effects).

3. Adherence is listed as a secondary outcome because it can greatly influence the results of a particular treatment regimen. Non-adherence is an issue in medicine and it would be useful to ascertain the scale of the problem- especially in CF patients, who already carry a substantial treatment burden. It reflects the patient's perspective of a particular intervention; for example, a significant rate of non-adherence may highlight issues regarding treatment tolerability and quality of life.

d) Study Design

I chose to include RCTs, quasi-RCTs and crossover trials for this review. The reasoning for this is discussed in the "Study Design" section in Chapter 4.

5.4 Search methods

Due to the similarities between the two reviews, I decided (with the advice of the Cochrane information specialist, NH) that it was possible to use one search strategy to find eligible studies for either review. This meant that throughout the screening process, I was able to accept titles and abstracts that matched the eligibility criteria for either review. Thereafter, I sorted through the chosen studies and allocated them to the most

suitable review. For this review, I searched the same medical databases and online registries as described in Chapter 4.

5.4.1 Examination of full text reports

After searching the medical databases and online registries, there were 8 titles and abstracts that appeared to match the criteria for either review. This meant that I could go on to the next stage of screening the full-text copies of these studies.

5.5 Estimated Results and Discussion

As of early May 2017 (when full-text screening took place), the protocol, "Interventions for the treatment of DIOS" had not yet been approved for publication. Having the same search strategy as the review for prevention of DIOS meant that I could go through the 8 studies to assess their eligibility for this review, but I did not have permission to progress to full data extraction and analysis.

However, my estimation was that there would be only 1 study eligible for inclusion; furthermore, the study was only available as an abstract. It was a double-blinded, randomized crossover trial (163) conducted in 1992 that investigated the use of high and low doses of PERT for the treatment of DIOS. The abstract indirectly addressed one of my primary outcomes: the treatment failure rate (measured in the study as the number of episodes of acute DIOS), but did not present the actual data for this outcome. Overall, the abstract gave very little information about PERT for the treatment of DIOS.

The results so far for this Cochrane review demonstrate that there is a great lack of evidence for the treatment of DIOS, as proven by the fact that there is only a single study

which was conducted 25 years ago and is only available as an abstract. As with the review on the prevention of DIOS, I find these results extremely disappointing. I will not be able to conduct a meta-analysis for this review and therefore will not be able to investigate the effectiveness and safety of various laxatives for the treatment of DIOS. I will draw my conclusions from these results and the results from the previous review (the prevention of DIOS) in chapter 7 of this thesis, but in summary- this unmistakable lack of evidence should alert clinicians to this poorly studied area of CF and will hopefully highlight an area for further research.

Chapter 6: The Management of Constipation and Distal Intestinal Obstruction Syndrome at CF Centres in the UK.

6.1 Introduction

In addition to undertaking a Cochrane Systematic Review, we thought it would be useful to determine the current UK practice for the treatment of constipation, incomplete DIOS and complete DIOS in children and adults with CF. We suspected that there may be differences in opinion and practice, due to limited evidence found in the literature search and also in the Cochrane review. We thought it would be helpful to establish the extent of these differences and also identify the management strategies that clinicians tend to favour.

To investigate this, I designed and distributed two online surveys that were sent out to paediatricians and adult physicians in UK CF centres. The surveys were based around patients with constipation, incomplete DIOS or complete DIOS. In this chapter, I will describe the methods used to produce and distribute the survey. I will then summarise the results of the survey and discuss the significance of these findings. The formal report of this survey can be found in **Appendix 5.**

6.2 Methods

6.2.1 Audience

Our target audience consisted of paediatric and adult consultants from the main CF centres in the UK. The centres were found on the CF Trust Directory in the annual data report (8). I constructed a list of consultants for each survey by using the CF Trust directory and individual trust websites. I obtained email addresses using existing contact lists from FG or WC, hand-searched the name of consultant and their base-centre.
The total number of contacts generated for the paediatric and adult surveys were 82 and 65 respectively. These contacts came from 29 different CF centres across the UK.

6.2.2 Survey questions

The surveys were based around short case vignettes about patients (either a child or adult, depending on the survey) with constipation, incomplete DIOS and complete DIOS. FG and WC guided me in the patient descriptions, as they were the experts in the field of CF. I then edited the phrasing and structure of questions and ensured that all the main laxatives were available in the list of treatment regimens. Case vignettes were chosen in order to make the questions more clinically relevant and to obtain more accurate answers about how clinicians really manage their patients. I thought that this would be more effective than simply asking the clinicians for the management of constipation and DIOS, where they may have selected the option(s) they thought were correct, rather than what they would actually do.
The DIOS questions were split into two parts to ascertain both first-line and second-line treatments. For the second-line treatment question, the consultants were given four

options: they could continue the existing treatment at the same dose, increase the dose of the existing treatment, add in another treatment or replace the existing treatment with a different regimen. If the consultants chose to add in another treatment or replace the existing treatment with another, they had to specify what these new treatments would be.

At the end of each survey, the consultants were also asked about the clinical features they would expect to find if the patient required surgical intervention for DIOS.

The survey was designed so that the questions were multiple-choice in style, but the consultants could select however many options they deemed necessary. There was also an opportunity to write comments in an additional box designated, "other" if the consultants required an option that was not already listed. The reason for constructing these surveys in such an open manner was to not restrict the consultants at all in their treatment plans. I hypothesised that the results would be more honest and reflective of current clinical practice if done in this way.

After each main section of the survey (i.e. constipation or DIOS), a follow-up question enquired whether the treatment decisions for each condition were based on personal experience, local guideline, low quality evidence (consensus, expert opinion, case reports) high quality evidence (systematic reviews, randomised control trials) or a combination of these options. The reason for including this question was to establish how many consultants had a good quality evidence base for their clinical decisions.

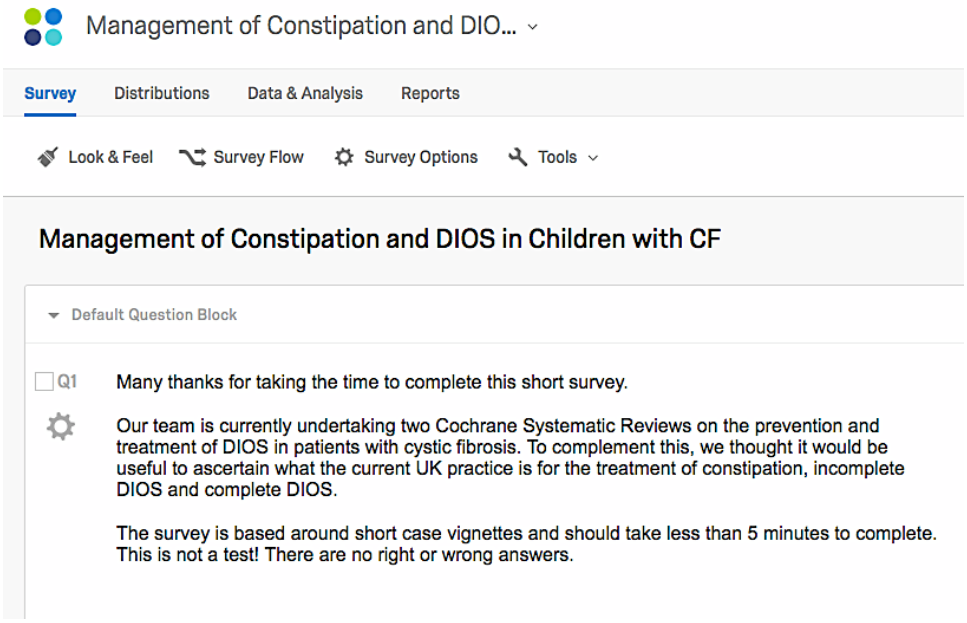
Extracts from the Paediatric survey can be found in **Appendix 4**.

6.2.3 Use of software

I generated the surveys using the Qualtrics© software (168) a website that enables the user to collect data on a specific subject by creating their own survey.

FG showed me how to navigate the software so that I could edit the survey. For example, the "Look and Feel" icon allowed me to alter the font, colour and format of the questions so that they appeared clearer to the user. The "Survey flow" icon helped me to change the order and add in extra components of questions, which was useful for follow-on questions that were dependent on user's previous answer. For the distribution of surveys, I generated web links for each consultant so that individual responses were recorded. Qualtrics© enabled me to visualise each consultant's response and the overall response for each question. These various tools available on the Qualtrics© software are shown below in Figure 6.1:

Figure 6.1: The editing features available on the Qualtrics© software:



The icons mentioned e.g. "Look and Feel" and "Survey Flow" can be seen in the image.

6.2.4 Survey distribution

As mentioned, Qualtrics© enabled me to generate individual web links for each consultant using their email addresses. All consultants received an email and could click on their personalised web link to complete the survey. Their responses were recorded in the results and data analysis section of Qualtrics©. The paediatricians were first emailed on 07/02/2017. Those who had not completed the survey were sent reminder emails on 20/02/2017. The adult physicians were emailed on 20/02/2017 and reminder emails were sent out to them on 01/03/2017.

6.3 Results

6.3.1 Data collection

On 08/03/2017 (one week after sending out the final reminder emails), I collected the survey responses from Qualtrics© and constructed two spreadsheets to summarise the data from either survey. I calculated two different percentages for each treatment option: how often the treatment was used as a single-drug regimen (i.e. on its own) and how often it was used as either a single-drug or in a multi-drug regimen (i.e. more than one approach was used).

20 different CF centres contributed to the results of the children's survey (out of a possible 28) and 21 different centres contributed to the results of the adult's survey (out of a possible 24). In total, 51% (42/82) paediatricians and 60% (39/65) adult physicians responded to the survey. However, the response rates for the questions on DIOS were lower than this (see section 6.4 and 6.5).

6.3.2 Data analysis

After I completed data collection, FG used STATA version 12.0 (169) for data analysis. For tests of proportions we used the chi-squared test and for comparison of continuous data we used student's t test or the Mann Whitney U test for normally distributed and non-normally distributed data respectively.

The statistical analysis of the results is shown in the formal report of the survey in **Appendix 5.** In the sections below, I will describe and compare the responses from both surveys, using the original result data from Qualtrics© and the percentages I calculated from Edexcel. I will round each percentage to the nearest whole number. Later in this chapter, I will discuss and the main findings from the results.

6.3.3 Constipation

42 paediatric consultants and 39 adult consultants responded to the question on the first-line management of constipation. The paediatric survey recorded 9 different treatment regimens, compared to 22 different regimens in the adult survey.

In both surveys, Movicol® was the most commonly used treatment option.

a) Constipation: Paediatric first-line treatments

When used as a single- treatment regimen, Movicol comprised almost 59% (24/42) responses in the paediatric survey. In total, Movicol® was included in 83% (35/42) paediatric regimens, either as a single-drug or as part of a multi-drug regimen.

Lactulose was another commonly used drug in the paediatric survey. Nearly 22% (9/42) consultants included it in their treatment plan for constipation, either on its own or alongside other treatments.

b) Constipation: Adult first-line treatments

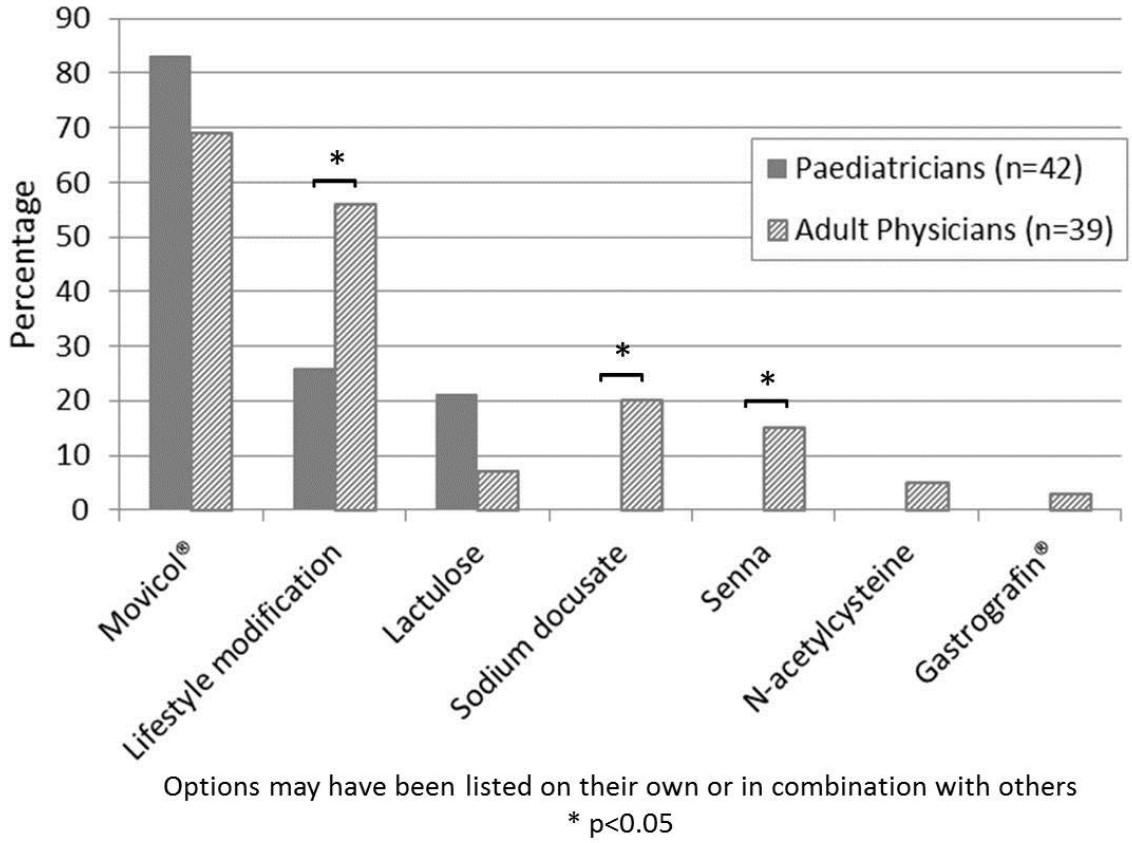
Movicol was used in nearly 21% (8/39) single drug regimens and in 69% (27/39) of either single-drug or multi-drug adult regimens.

Overall, wide ranges of treatments were used to treat adult constipation. Some consultants (7%, 3/39) chose to use lifestyle modifications as a single treatment. However, it also featured considerably as part of treatment regimens with other drugs. In total, over 56% (22/39) adult physicians used lifestyle modifications as either as a single-treatment or as part of a larger regimen.

For treatments used on their own or as part of a multi-drug regimen, Sodium docusate featured in nearly 21% (8/39) of responses, Senna was in over 15% (6/39) regimens and N-acetylcysteine was chosen on two occasions (2/39). Gastrografin® was used once (1/39) as a single-drug treatment. Unlike the paediatric survey, Lactulose did not feature in the adult treatments at all.

In the box designated, “other” (where consultants could contribute additional comments) 4/39 adult physicians decided to send the patient for an abdominal x-ray.

Figure 6.2: First-line treatment for constipation



(Options may have been listed on their own or in combination with others)

6.3.4 Incomplete DIOS

There were 37 responses from the adult consultants and 39 responses from the paediatric consultants for the questions on the treatment for incomplete DIOS. The treatment regimens chosen for incomplete DIOS varied greatly.

In the adult survey, there were 23 different 1st line treatment plans and 25 different 2nd line treatment plans for incomplete DIOS.

For the children's survey, there were 22 different treatment combinations for 1st line management and 27 different combinations for 2nd line management of incomplete DIOS.

Incomplete DIOS: Paediatric first-line treatments

Movicol® and Gastrografin® were equally common for a single-drug 1st line management, each used on their own in 15% (6/39) cases. In total (either in a single-drug or multi-drug regimen), Movicol® was used for 56% (22/39) 1st line combinations and Gastrografin® was used in 26% (10/39).

Another commonly used 1st line drug was Lactulose, featuring 21% (8/39) times, either in a single or multi-drug regimen. In total, N-acetylcysteine was used in 13% (5/39) 1st line cases and Sodium picosulphate and Klean-Prep® were used in 5% (2/39) 1st line regimens. The least used drugs were Senna and Sodium docusate, featuring in 2% (1/39) regimens each.

Incomplete DIOS: Adult first-line treatments

16% (6/37) adult consultants decided to use Gastrografin® on its own for 1st line treatment, which accounted for the largest percentage of any single drug regimen.

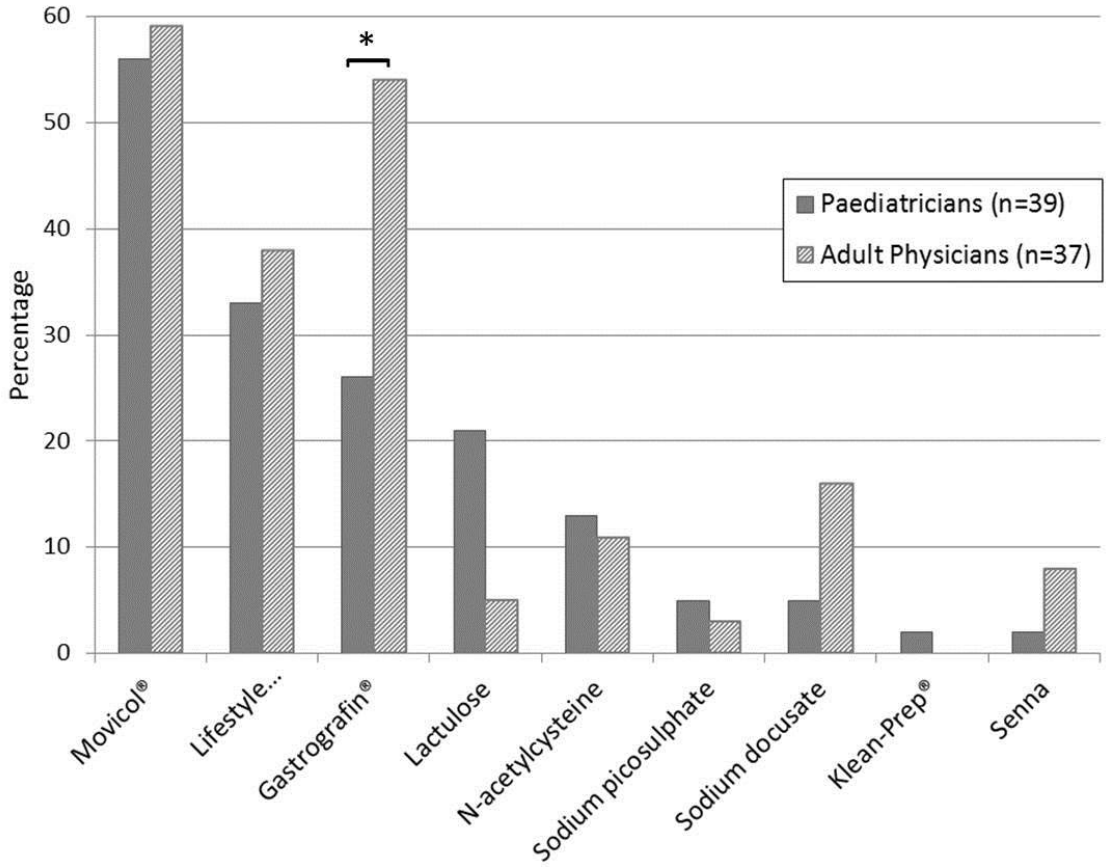
In total, (as a single drug or in a multi-drug combination) Gastrografin® was included in 54% (20/37) 1st line treatment regimens. Another commonly used drug was Movicol®, used in nearly 60% (22/37) 1st line adult treatment regimens, as a single drug or in a combination. Lifestyle modifications featured in nearly 38% (14/37) 1st line treatment regimens.

Many other laxatives were also chosen, such as Sodium docusate (used in 6/37 or 16% single drug or multi-drug combinations), N-acetylcysteine (in 4/37 or 11% single drug or multi-drug combinations) and Senna (in 3/37 or 8% single drug or multi-drug combinations).

The drugs least used were Lactulose (2/37 single drug or multi-drug combinations) and Sodium picosulphate (1/37 single drug or multi-drug combinations).

4 consultants (10.8%) also chose to add imaging to their regimen. An abdominal ultrasound scan was chosen on two occasions, a CT scan was used once and an abdominal x-ray was also used once.

Figure 6.3: First-line treatments for incomplete DIOS:



Options may have been listed on their own or in combination with others
* p<0.05

(Options may have been listed on their own or in combination with others).

6.3.5 Complete DIOS

In the adult survey, 36 consultants answered the questions on 1st line management for complete DIOS and 35 answered the questions for 2nd line treatment. There were 25 different 1st line treatment regimens and 26 different 2nd line regimens.

In the children's survey, 38 answered the questions on 1st line management and 36 consultants answered the questions on 2nd line management for complete DIOS. There were 17 different 1st line treatment regimens and 23 different 2nd line treatment regimens.

Complete DIOS: Paediatric first-line treatment

In the paediatric survey, the most common intervention was surgical review, featuring 21% (8/38) times on its own and 68% (26/38) times as part of a larger treatment regimen. Gastrografin® was the most commonly used drug, featuring 16% (6/38) times as a single-drug regimen and 53% (20/38) times in total as part of larger regimens. Klean-Prep® was also used frequently. It was chosen in 29% (11/38) regimens, either in a single or multi-drug regimen.

24% (9/38) consultants used some or all parts of the conventional "drip and suck" management for bowel obstruction (intravenous fluids, nasogastric tube, nil by mouth). Less common interventions included N-acetylcysteine (in 5% or 2/38 regimens) and an enema (1/38 regimens). 1 consultant also chose to include antibiotics in their 1st line management for complete DIOS.

Complete DIOS: Adult first-line treatment

The commonest 1st line single-drug regimens were Gastrografin® and Klean-prep®, each accounting for 11% (4/36). However, 72% (26/36) 1st line regimens included Gastrografin® and 50% (18/36) included Klean-prep® as part of single-drug or multi-drug regimens.

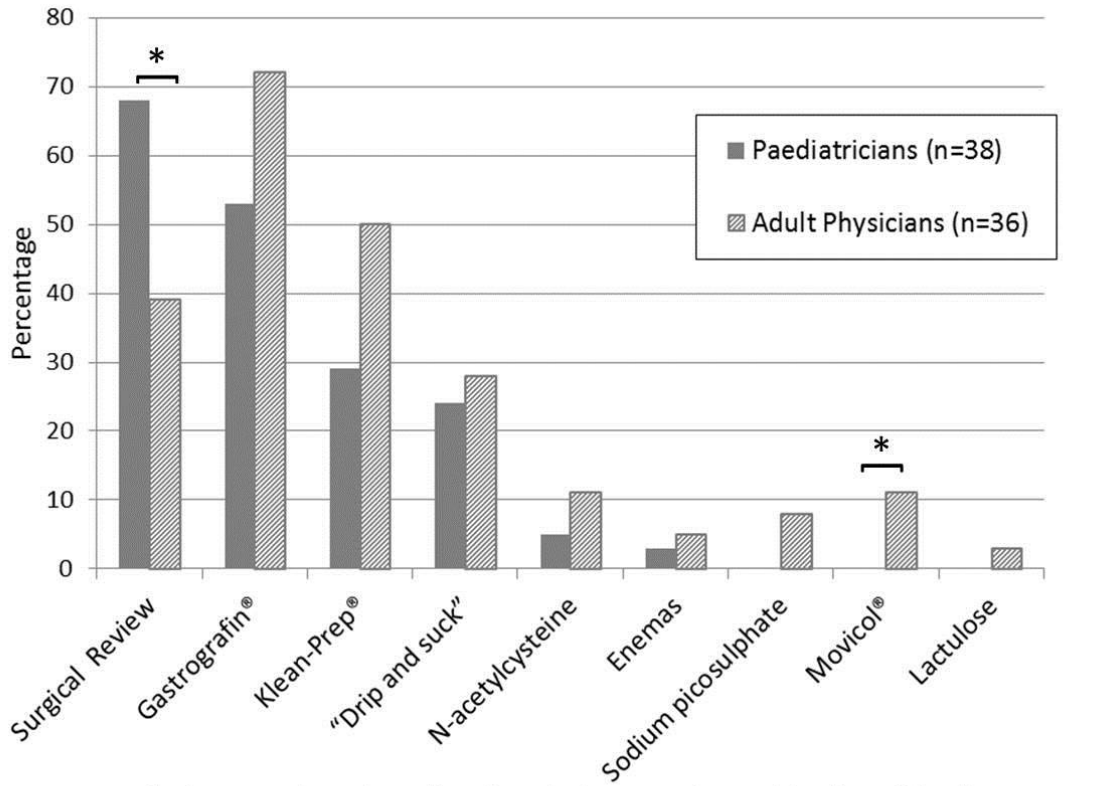
A significant number (39% or 14/36) of consultants included surgical review in their 1st line management of complete DIOS. 28% (10/36) also chose to include some or all parts

of the conventional “drip and suck” management for bowel obstruction (intravenous fluids, nasogastric tube, nil by mouth and 17% (6/36) consultants decided to refer the patient for a CT scan.

More invasive methods were also used: 6% (2/36) clinicians chose to send the patient for a colonoscopy, and the same percentage also suggested an enema as part of the 1st line management.

Other laxatives were less commonly used in 1st line regimens. N-acetylcysteine and Movicol® were each used 11% (4/36) times as a single or multi-drug regimen, Sodium picosulphate was used in 8% (3/36) regimens and Lactulose was used in 3% (1/36).

Figure 6.4: First-line treatments for complete DIOS:



Options may have been listed on their own or in combination with others.
“Drip and suck” includes mention of nil by mouth, intravenous fluids or nasogastric tube.
* p<0.05

(Options may have been listed on their own or in combination with others).

6.3.6 Reasons for a surgical review in DIOS

Towards the end of the survey, the consultants were asked which clinical features in complete DIOS would prompt them to ask for a surgical review. Again, they could select as many options as they deemed necessary. There were some similarities between the two surveys. 97% (37/38) paediatricians and 89% (32/36) adult physicians selected rebound tenderness and guarding. Evidence of suspected perforation on abdominal imaging was also very popular, selected 94% (34/36) times by the adults and 100% (38/38) times in the paediatric survey. However, there was a great disparity between bilious vomiting, voted 33% (12/36) times by adult physicians and 95% (36/38) times by paediatricians.

Failure to improve with medical therapy after 24 hours also showed a big difference in opinion between the two surveys, selected 17% (6/36) times by adult consultants and 42% (16/38) times by paediatricians. Failure to improve after 48-72 hours was selected 44% (16/36) times by the adult consultants and 50% (19/38) times by the paediatricians, failure to improve after 96 hours was selected 17% (6/36) by adult consultants and 11% (4/38) by the paediatricians.

6.3.7 Evidence base for decisions

The adult and paediatric consultants were asked how they were guided to make decisions about the treatments for constipation and DIOS.

Evidence base for constipation treatment

For the decision on the treatment of constipation, 100% (39/39) adult consultants and 88% (38/43) paediatric consultants used personal experience to make their decision. 31%

(12/39) adult consultants and 49% (21/43) paediatricians used local guideline, 33% (13/39) adult consultants and 42% (18/43) paediatricians used low quality evidence. No consultants used high quality evidence in their decisions for constipation treatment.

Evidence base for DIOS treatment

For the treatment of DIOS, 100% (36/36) adult consultants and 87% (33/38) paediatricians used their personal experience, 58% (21/36) adult consultants and 74% (28/38) paediatricians used their local guideline and 61% (22/36) adult consultants and 58% (22/38) paediatricians used low quality evidence. Only 3% (1/38) paediatricians said they would use high quality evidence to make decisions about DIOS management.

6.4 Discussion

6.4.1 Main findings

The results of the survey showed that there is a huge difference of approach for the treatment of constipation, incomplete DIOS and complete DIOS in patients with CF, with particular variation for the treatment of DIOS.

a) Constipation

The treatment of constipation showed moderate variation, which was particularly demonstrated in the adult survey, where physicians used 22 different combinations. However, the paediatricians only used 9 different combinations. It is also important to note that the response rate for the questions on constipation was higher than the questions on DIOS, which may reflect in the number of combinations used. Movicol® featured significantly in the treatment combinations for constipation in both surveys. It was used in 69% adult regimens and 83% paediatric regimens. However, adult physicians were more likely to use lifestyle modifications than the paediatricians and also used a higher mean number of interventions per patient.

b) Incomplete DIOS

The treatment of incomplete DIOS displayed the greatest variation out of all the questions. Paediatricians used 22 different 1st line and 25 different 2nd line treatment combinations and adult physicians used 23 different 1st line and 27 different 2nd line treatment combinations. In both surveys, Movicol® and Gastrografin® were the most commonly used drugs for 1st line treatment. However, the adult physicians used more Gastrografin® than the paediatricians.

c) Complete DIOS

For complete DIOS, adult physicians showed the most variation, using 25 different 1st line and 26 different 2nd line combinations. Paediatricians also displayed a fair amount of variation, with 17 different 1st line and 23 different 2nd line treatment combinations. Gastrografin® and Klean-Prep® were the most commonly used 1st line treatments for the adult survey, but paediatricians opted for surgical review as the top choice for 1st line treatment, follow by Gastrografin®.

6.4.2 Strengths of the survey

FG, WC and I designed the survey so that the average respondent would take less than 5 minutes to complete the questions. Short surveys are generally favourable because the audience do not have to sacrifice a great deal of time to answer questions. After reviewing all the questions in the draft survey, I also helped to eliminate some non-essential questions in order to shorten the duration time.

The questions were based around clinical cases similar to those seen in real patients and we used terminology that the consultants would be familiar with e.g. “right-iliac fossa mass”. I helped FG and WC to improve the phrasing and structure of the questions so that they were clear and more succinct.

I also ensured that the respondents could select however many treatment options they deemed necessary. As the respondents were not restricted in their choices, it is likely that the answers were more accurate. Adding a box underneath the options labelled, “other” for respondents to write additional options or comments, enhanced this.

Before distribution, WC and I tested the survey by answering the questions ourselves. This gave us an opportunity to amend any errors and rephrase sentences that were not clear.

In order to improve the response rate, I sent out reminder emails one week after the first survey distribution. I was aware that emails might have been lost in the many correspondences of some consultants and others were on annual leave at the time of the first email.

6.4.3 Survey limitations

This survey did not include countries outside the four devolved nations of the UK. However, given the disagreements within one country with a unified training program and clinicians who all follow the same guideline, it is unlikely that there is more agreement elsewhere in the world.

Although I sent emails to all the main CF centres in the UK, there were some centres that did not complete the survey. For the adult survey, these centres were: London (South), Nottingham and Edinburgh. For the paediatric survey, these centres were: Leeds, London (South), Newcastle upon Tyne, Sheffield, Aberdeen, Dundee, Lanarkshire and Cardiff. It would have been preferable to have at least one response from each centre, but I realised that this would have been difficult to achieve in practice. Ultimately, I collected responses from 21/24 adult centres and 20/28 paediatric centres. I deemed these to sufficiently represent the treatment approaches used across the UK.

6.4.4 Differences in approach: Paediatricians compared to adult physicians

The survey revealed obvious differences in approach between paediatricians and adult physicians, particularly demonstrated in their choice of laxatives for incomplete DIOS and in their approaches to surgical review for complete DIOS.

Adult physicians were more likely to use bowel cleansers such as Gastrografin® to treat incomplete DIOS, whereas paediatricians tended to use Movicol® and treated incomplete DIOS as they would for constipation. The pathophysiology and clinical diagnoses for constipation and DIOS are distinct (102), so I believe they should be treated as separate conditions. It is likely that adult physicians have more clinical experience in treating patients with DIOS (it tends to be more common in adulthood) (91) so they may recognise that it is distinct from constipation and treat it with a bowel cleanser instead of an osmotic laxative.

The second big difference between adult physicians and paediatricians was the extent at which they relied on surgical review for the treatment of complete DIOS. 68% paediatricians chose to include a surgical review in their 1st line management for complete DIOS, compared to only 39% adult physicians. Paediatricians also had a lower threshold for sending their patients for a surgical review, with 95% paediatricians requesting a surgeon for bilious vomiting, compared to 33% adult physicians. 42% paediatricians would also call a surgeon if their patient had not improved on medical therapy after 24 hours, compared to 17% adult physicians.

It may be that these results demonstrate predictable differences in approach between paediatric and adult medicine, where paediatricians have a lower threshold for surgical

intervention due to pressure put on them from anxious parents. However, it is more likely that these results suggest that paediatricians have less confidence in dealing with acute bowel obstruction than their adult colleagues, as the incidence of DIOS is reportedly lower in children than in adults (8). These findings are supported by the literature, as Munck (111) also found that children were more likely to receive surgical intervention than adults.

6.4.5 Lack of Consensus

On average, the treatment for incomplete DIOS showed the greatest amount of variation, with many consultants treating incomplete DIOS the same as they would for constipation. This highlights an area of insufficient knowledge, experience (as explained above) compounded by the fact that constipation and incomplete DIOS are sometimes difficult to clinically distinguish from one another in practice. Although there are criteria for differentiating constipation from incomplete DIOS (102), the margins between them are sometimes blurred when faced with an individual patient.

The lack of certainty in treating DIOS is also driven by a great lack of evidence. This was reflected in the survey where over 99% consultants recognised the scarcity of high-quality evidence. There are no national or international evidence-based guidelines for the treatment of DIOS, but there are evidence-based guidelines for the treatment of constipation (101), which could be a reason for the lower number of combinations used for constipation. However, it is important to note that the guidelines for constipation do not advocate the use of Movicol® (the most common constipation treatment in this survey) for patients with CF. Therefore, caution should be taken when extrapolating these guidelines to include the use of Movicol® for CF constipation.

Furthermore, I believe that the variation in DIOS management is precipitated by the lack of Patient Reported Outcome Measures (PROMs) and Magnetic Resonance Imaging (MRI) scans, which comes from a lack of evidence on these resources. If these were commonly used, they may well advance the diagnostic process of DIOS and provide information about the quality of care delivered to patients.

Chapter 7: Conclusions

7.1 Main findings from thesis

During my reading, I discovered that DIOS is a common condition in CF (109, 110) and if it progresses to complete intestinal obstruction, can also be a life threatening condition. It is therefore rational to expect that such a significant problem should have robust evidence for its treatment and prevention. However, throughout my literature review, I could not find any set guidelines for the prevention or for the treatment of DIOS. The ESPGHAN CF working group set clear criteria regarding the clinical diagnosis of DIOS (102), but the information for the management of DIOS was extremely vague and only based on case studies and anecdotal evidence.

Before starting the Cochrane review, I considered that the scarcity of evidence on DIOS reflects how little importance is placed on gastrointestinal problems in CF. Conversely, there are a staggering number of randomised controlled trials on the respiratory complications in CF. This is likely the case because CF patients predominantly suffer from respiratory complications and are most likely to die from respiratory failure. However, as explained in my literature review, all complications in CF affect the overall health of the patient. If gastrointestinal problems such as constipation and DIOS are not managed effectively, they may worsen the patient's quality of life, nutritional status, mobility, and ultimately make them more susceptible to respiratory infections. It is therefore imperative that these problems are placed at a higher level of importance.

After these findings in my literature review, my aim for this thesis was to determine the current evidence and practice for the management of DIOS. From this, I had two

objectives: to conduct a Cochrane systematic review to evaluate the evidence and create a survey to evaluate current practice.

The Cochrane review revealed a huge lack of evidence for the prevention of DIOS in CF. Only one study was eligible for inclusion, so I was unable to compare the safety and efficacies of different interventions. This also meant that I was unable perform a meta-analysis to assess the consistency and reliability of the results. In addition, the included study was downgraded in quality for various reasons, did not assess the use of a typical laxative agent and drug in question is no longer licenced for use in the UK.

The limited findings from the review suggested the importance of patient-reported symptom scores, which may provide information about the tolerability and overall effects of an intervention. However, this was poorly demonstrated in such a small number of participants.

The unfinished Cochrane review, "Interventions for the treatment of DIOS" also showed that there is most likely a deficiency of evidence for the treatment of DIOS in CF. From the full-text screen, I judged that there was only one eligible abstract which contributed a limited amount of data.

The survey demonstrated a lack of consensus and therefore a lack of evidence for the treatment of incomplete DIOS and complete DIOS. It seems that many clinicians have difficulty diagnosing incomplete DIOS in clinical practice (as they treated incomplete DIOS exactly as they would for constipation) and nearly all have acknowledged the lack of clear evidence for the treatment of DIOS. Furthermore, there are differences in approach between paediatricians and adult physicians in their choice of laxative, with adult physicians more likely to use a more potent bowel cleanser to treat incomplete DIOS,

whereas paediatricians mostly used Movicol®. In addition, paediatricians were far more likely to request a surgical review than adult physicians. These differences most likely relate to their degree of experience in treating DIOS.

7.2 Implications for future practice

The results of the survey and review should signal that there is no consensus or evidence-base for the management of DIOS in clinical practice. As mentioned, there is a great deal of importance placed on respiratory complications in CF, but not enough on the gastrointestinal problems that commonly arise. This was not only proven by the results of the review; the survey also highlighted the confusion that can occur between constipation and incomplete DIOS, as many clinicians treated them as though they were the same complication.

However, one must appreciate that it is sometimes difficult to distinguish these complications from one another in clinical practice. With that said, I believe the use of abdominal imaging may be important in the management of DIOS. This featured as an outcome measure in the review and was mentioned in the survey's discussion. Abdominal imaging e.g. MRI could be used to aid the diagnosis of DIOS and also act as a measure of treatment efficacy. The unclear clinical distinction between constipation and incomplete DIOS could be alleviated by the use of imaging. Furthermore, abdominal imaging could be used as a marker for the treatment of DIOS; clinicians could assess the efficacy of various laxative agents by comparing patients imaging results.

It is also worth noting that the review highlighted the use of patient-reported symptom scores. These are important in clinical practice for understanding how patients experience and tolerate their treatments. The significance of patient reported outcome measures was also highlighted in the discussion of the survey; they could enhance the quality of care delivered to patients. For example, PROMs may be used to investigate the palatability of various laxative agents used for treating constipation and DIOS, which could provide important information about their tolerability. Overall, patient feedback could lead to better communication and hence, improve patient satisfaction and adherence.

7.3 Implications for future research

As there was only one low quality, crossover trial eligible for inclusion in the systematic review, it is evident that there is a great need for more research in this area. My findings were also reflected in the survey, where 99% clinicians recognised that there is a lack of high quality evidence for the treatment of incomplete and complete DIOS. Future trials should also include larger numbers of participants for more precision and be designed as placebo-controlled, randomised- controlled trials in order to provide robust evidence. Following on from the limited findings of the review, it would be very interesting to look at the role of prokinetics for the prevention or treatment of DIOS. Although cisapride has been removed from the UK drug market, there are many other types of prokinetics such as domperidone and metoclopramide, as well as antibiotics with prokinetic properties such as erythromycin and azithromycin. Azithromycin is commonly used for respiratory complications in CF, so it would be interesting to see whether the incidence of DIOS in

patients taking azithromycin is significantly different to those not taking it. An observational study using data from the UK CF registry could help obtain this information. Of course, there are various factors that may affect the incidence of DIOS; patients who take regular azithromycin arguably have a lower standard of health and may be more likely to suffer from gastrointestinal complications, such as DIOS. However, these types of factors could be accounted for in subgroup analyses, for example, grouping patients according to their %FEV1. In summary, the lack of evidence on this subject has opened up various avenues for further research. After the Cochrane review demonstrated the use of prokinetics for the prevention of DIOS (albeit in a very limited way), I believe the next logical step is to further investigate their role in the management of DIOS.

Chapter 8: Reflections on intercalating

Before starting my fourth year in medical school, I had originally planned to carry on to fifth year without intercalating because I had not found a course that had sparked my interest. This changed after I did some further research and discovered the MPhil in CF, led by Dr Gilchrist. I was delighted that the MPhil was on such a fascinating and complex subject in which I could truly immerse myself. During my previous medical school placements I had also developed an enthusiasm for paediatrics; consequently I was pleased that the MPhil would involve working closely with the paediatric department at the hospital. But above all, I was eager to learn the skills involved in research so that in my future career I could add value and contribute to a subject that I feel passionately about.

When I discovered that I would be an author of a Cochrane review, my initial reaction was that of surprise. I had no previous experience in systematic reviews or meta-analysis methods other than the few lectures I had attended in medical school. The prospect was rather overwhelming. I remedied my lack of knowledge by attending a 4-part training course on Cochrane reviews, which helped me gain some understanding. However, the course provided a large amount of information in a relatively short period of time, which meant that I forgot some of the material. It was really when I began working on the review that I gained a better understanding. This was supplemented by the countless questions I asked our managing editor (NJ) and I will be eternally grateful for her patience and support. I also watched several Cochrane webinars and attempted to gain as much knowledge as I could from the Cochrane handbook. Although I struggled at times to

comprehend these new skills, in retrospect I enjoyed the steep learning curve. I also valued being able to work independently and in depth on something that I could take my time over; I was often unable to do this during the hectic life of medical school.

When it came to writing the thesis, I initially found the process to be quite difficult. I have always loved writing and I undoubtedly underestimated the task of writing such a long piece of work. I quickly realized that a thesis requires a particular style, structure and requires a great deal of planning. However, after careful organisation and devoting sufficient time to writing, it was very achievable.

After all the time and effort I had devoted to gain an understanding of the methodology involved in a Cochrane review, I found it very frustrating that I was unable to perform a meta-analysis for the review. This initially led me to be overly optimistic about the inclusion of another study. In hindsight, I was so eager to compare two studies that I had overlooked the risk of bias for the second study. Ultimately, I realised that there is no point in producing a review if it includes poor studies that do not fit the review's rationale. And although I had not been able to perform a meta-analysis, I had still gained valuable skills that could be used for future reviews. In addition, my review identified gaps in the literature that would highlight areas for future research.

Overall, I have gained a great deal of knowledge and experience from this MPhil. I now know what is involved in a Cochrane review and learned valuable skills from being part of one. After helping to write a protocol and responding to peer review comments on it, I now understand the criteria required to produce an effective protocol. I have learnt what

makes a comprehensive search strategy and how to navigate my way around online medical databases. After screening studies, extracting data and assessing studies for quality, I have vastly improved my skills for critical appraisal. I now understand the important points to consider when analysing data e.g. directness, precision and consistency and have produced a Summary of Findings table to illustrate this. Although I did not perform a meta-analysis, I have learnt a great deal about the tests and processes required to perform one. In addition, I have learnt how to use the software needed produce a Cochrane review e.g. RevMan, Covidence, GRADE.

Generally, being able to examine intervention studies and understand areas that may downgrade or upgrade evidence has given me a useful set of skills for my future practice. Towards the end of my MPhil, I also contributed to a protocol proposal for the next MPhil student (who will be in the department from September 2017). I found this to be a valuable experience because I did not have the opportunity to contribute to the proposal for my own review protocol; this therefore completed my holistic "Cochrane experience".

Furthermore, in contributing to the production and distribution of a survey, I now understand the important points to consider when writing a questionnaire. And after distributing and collecting a large amount of data, I now have a greater appreciation of the work involved in generating a survey.

Clinically, I had almost no knowledge of DIOS before starting this academic year. After attending weekly CF clinics and writing my literature review, I now have a far greater understanding about DIOS and CF in general. I also have great appreciation and understanding about how an MDT works. I found that talking to and shadowing different professionals involved in CF care (other than physicians) was a very valuable experience;

it is not often that medical students get to spend an extended period of time with professionals such as physiotherapists, dieticians, social workers and psychologists.

In conclusion, I have gained much knowledge and experience from my year as an MPhil student. I feel proud to have been part of a Cochrane review that will be published and provide important information for clinicians and will highlight areas for future research. I am also proud to have been part of a nationwide survey that has revealed significant information about the current treatments used for DIOS. I am optimistic about the publication of this survey report. My hard work has given me confidence and motivation to engage in more academia and research in my future career. Working closely with the CF team has also furthered my passion to pursue a career in paediatrics.

Chapter 9: Reflections after the Viva

Two weeks after handing in my thesis, my work and comprehension of the subject were assessed in a viva. I was unsure about what to expect and felt rather apprehensive about it. Dr Carroll led me through a mock examination beforehand, which really helped me to prepare for potential questions; I would like to take this opportunity to thank him for his guidance and support.

On the day of the viva, my feelings of apprehension evaporated as I was called into the room. The examiners were warm, friendly and seemed genuinely eager to discuss my thesis with me. This made me feel very much at ease. The calm atmosphere meant that I felt confident enough to have some in-depth discussions with the examiners and showcase my knowledge. After the viva, I was delighted to have been awarded recommendation 2, an indication that my hard work had paid off.

The most significant learning point from the viva was how important it is to improve and enhance my work to make it the best it can be. After 4 years in medical school, I became more familiar with sitting one exam and being awarded a final result. It was refreshing to be able to re-visit my work after the viva and look at it through new eyes.

A specific learning point from the viva was that I should write my discussion with more conviction. The examiners wanted me to be incisive about the fact that there is no evidence for the management of DIOS; they felt that I was “holding back” at times in my writing. This point led me to reflect on my overall confidence in decision-making and it made me realise that I can sometimes be hesitant in making bold statements, even when

I am correct. The examiners had told me that I spoke well and with conviction in the viva, so I wondered why I had not done so in my writing. This is obviously something I need to be aware of in the future: I should not only be confident when defending my work, but should be assertive in my decision from the outset.

Another interesting topic from the viva was discussing the implications of my thesis for future research. There are many possibilities, (since the Cochrane review proved that there was a serious lack of evidence) but Dr Carroll and I had already discussed the potential role for prokinetics in the management of DIOS, following on from the limited findings in the review. It was exciting to propose this idea in the viva because Professor Lenney, Dr Hurley and I were able to debate the practicalities of conducting a study on this topic. For example, a study investigating the role of azithromycin (an antibiotic with prokinetic properties) could assess the patient's pulmonary function (e.g. %FEV1) as a primary outcome and assess the incidence of DIOS as a secondary outcome. A limitation of this study would likely be the correlation of a patient's poor lung function and declining health with their chance of having DIOS. After discussing these points with the examiners, I was further motivated to explore the role of prokinetics in DIOS.

Overall, the viva was a very useful experience. It gave me to opportunity to challenge myself and openly discuss my thoughts on the work I had done and its implications for future research. It has also given me the confidence to be more assertive in my decisions, which is something I will take with me in my future work. I would like to thank Professor Lenney and Dr Hurley for taking the time to examine me and making me feel at ease. I would also like to thank Professor Pandyan for being the independent chair and for welcoming me so warmly to the examination.

Chapter 10: References

(1) Zhang X, Hothi J, Zang Y, Srinivasan S, Stokes D, Zhang W. c.3623G > A mutation encodes a CFTR protein with impaired channel function. Respiratory Research 2016;17(8):1-6.

(2) Busch R. On the history of cystic mucoviscidosis. Deutche Gesundhs 1978;33:316-320.

(3) Busch R. On the history of cystic fibrosis. Acta Univ Carol Med 1990;36:13-15.

(4) Littlewood J. The History of Cystic Fibrosis. 2016; Available at: http://www.cfmedicine.com/history/earlyyears.htm. Accessed November, 2016.

(5) Gee S. On the coailac affection. St Bartholomew's Hospital Report 1888;24:17-20.

(6) Andersen DH. Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease; a Clinical and Pathologic Study. Am J Dis Child 1938;56(2):344-399.

(7) Sant'Agnese PA, Darling RC, Perera G, A., Shea E. Sweat electrolyte disturbances associated with childhood pancreatic disease. Am J Med 1953;15(6):777-784.

(8) Carr S, Cosgriff R, Rajabzadeh-Heshejin V. UK Cystic Fibrosis Registry 2015 Annual Data Report. 2016; Available at: https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources. Accessed December 2016.

(9) Kerem B, Rommens J, Buchanan J, Markiewicz D, Cox T, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922):1073-1080.

(10) US Food and Drug Administration, (FDA). Kalydeco (ivacaftor) Information 2015; Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm323671.htm. Accessed November, 2016.

(11) Davies J, Alton E, Bush A. Cystic fibrosis. BMJ 2007;335(7632):1255-1259.

(12) Hull J, Thomson A. Genetics of Cystic Fibrosis. Curr Paediatr1994;4(3):136-138.

(13) Vankeerberghen A, Cuppens H, Cassiman J. The cystic fibrosis transmembrane conductance regulator: an intriguing protein with pleiotropic functions. J Cyst Fibros 2002;1(1):13-29.

(14) MacDonald K, McKenzie K, Zeitlin P. Cystic Fibrosis transmembrane regulatory proteins: "class" oppourtunity for novel drug innovation. Paediatr Drugs 2007;9(1):1-10.

(15) Welsh M, Smith A. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. Cell 1993;73(7):1251-1254

(16) Lissauer T, Carroll W editors. Illustrated Textbook of Paediatrics. 5th ed. London: Elsevier; 2017.

(17) Welsh M, Ramsey B, Accurso F, Cutting G. Part 21, Chapter 201: Cystic Fibrosis . In: Valle D, Beaudet A, Vogelstein B, Kinzler K, Antonarakis S, Ballabio A, et al, editors. The Metabolic and Molecular Bases of Inherited Disease New York: The McGraw-Hill Companies; 2004.

(18) Fanen P, Wohlhuter-Haddad A, Hinzpeter A. Genetics of cystic fibrosis: CFTR mutation classifications toward genotype-based CF therapies. Int. J of Biochem Cell Biol 2014;52:94-102.

(19) De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J. Cystic fibrosis: terminology and diagnostic algorithms. Thorax 2006;61(7):627-635.

(20) The Clinical and Functional TRanslation of CFTR, (CFTR2). Resources: FAQS. Available at: http://cftr2.org. Accessed December 2016.

(21) Armstrong D, Grimwood K, Carlin J. Lower airway inflammation in infants and young children with cystic fibrosis. Am J Respir Crit Care Med 1997;156(4):1197-1204.

(22) Dakin C, Numa A, Wang H. Inflammation, infection, and pulmonary function in infants and young children with cystic fibrosis. Am J Respir Crit Care Med 2002;165(7):904-910.

(23) Stoltz D, Meyerholz D, Pezzulo A. Cystic Fibrosis Pigs Develop Lung Disease and Exhibit Defective Bacterial Eradication at Birth. Sci Transl Med 2010;2(29):29-31.

(24) Clunes M, Boucher R. Cystic Fibrosis: The Mechanisms of Pathogenesis of an Inherited Lung Disorder. Drug Discov Today Dis Mech 2007;4(2):63-72.

(25) Goldman M, Anderson G, Stolzenberg E, Kari U, Zasloff M, Wilson J. Human beta-defensin-1 is a salt-sensitive antibiotic in lung that is inactivated in cystic fibrosis. Cell 1997;88(4):553-560.

(26) Knowles M, Robinson J, Wood R, Pue C, Mentz W, Wager G, et al. Ion composition of airway surface liquid of patients with cystic fibrosis as compared with normal and disease-control subjects. J Clin Invest 1997;100(10):2588-2595.

(27) Matsui H, Grubb BR, Tarran R, Randell SH, Gatzy JT, Davis CW, Boucher RC. Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. Cell. 1998;95:1005–15.

(28) Tarran R, Grubb BR, Gatzy JT, Davis CW, Boucher RC. The relative roles of passive surface forces and active ion transport in the modulation of airway surface liquid volume and composition. J Gen Physiol. 2001;118:223–36.

(29) Guilbault C, Saeed Z, Downey GP, Radzioch D. Cystic fibrosis mouse models. Am J Respir Cell Mol Biol. 2007;36:1–7.

(30) Pezzulo A, Tang X, Hoegger M. Reduced Airway Surface pH Impairs Bacterial Killing in the Porcine Cystic Fibrosis Lung. Nature 2012;487(7405):109-113.

(31) Chmiel J, Berger M, Konstan M. The role of inflammation in the pathophysiology of CF lung disease Clin Rev Allergy Immunol 2002;23(1):5-27.

(32) Hubeau C, Puchelle E, Gaillard D. Distinct pattern of immune cell population in the lung of human fetuses with cystic fibrosis. J Allergy Clin Immunol 2001108524–529.

(33) Khan T, Wagener J S, Bost T. *et al* Early pulmonary inflammation in infants with cystic fibrosis. Am J Respir Crit Care Med 19951511075–1082

(34) Stallings V, Stark L, Robinson K, Feranchak A, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108(5):832-839.

(35) Wilschanski M, Durie P. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut 2007;56(8):1153-1163.

(36) Sabharwal S. Gastrointestinal Manifestations of Cystic Fibrosis 2016;12(1):43-47. J Gastroenterol Hepatol 2016;12(1):43-47.

(37) Farrell P, Rosenstein B, White T, Accurso F, Castellani C, Cutting G, et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report. J Paediatr 2008;153(2):4-14.

(38) Eng W, LeGrys V, Schechter M, Laughon M, Barker P. Sweat-testing in preterm and full-term infants less than 6 weeks of age. Paediatr Pulmonol 2005;40(1):64-67.

(39) LeGrys V, Yankaskas J, Quittell L, Marshall B, Mogayzel PJ. Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. J Paediatr 2007;151(1):85-89.

(40) Mishra A, Greaves R, Massie J. The Relevance of Sweat Testing for the Diagnosis of Cystic Fibrosis in the Genomic Era. Clin Biochem Rev 2005;26(4):135-153.

(41) © Cystic Fibrosis Trust Registered Charity (England and Wales). How is cystic fibrosis diagnosed? 2017; Available at: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/diagnosis. Accessed March 2017.

(42) Dankert-Roelse J, Vernooij-van Langen A. Newborn screening for cystic fibrosis: pros and cons. Breathe Sep 2011;8(1):24-30.

(43) Rosenfeld M, Emerson J, McNamara S, Joubran K, Retsch-Bogart G, Graff GR, et al. Baseline Characteristics and Factors Associated With Nutritional and Pulmonary Status at Enrollment in the Cystic Fibrosis EPIC Observational Cohort. Pediatr Pulmonol 2010;45(9):934-944.

(44) Munck A, Mayell V, Winters A, Shawcross N, Derich R,; Parad J, Barben K, Southern W. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. ECFS Neonatal Screening Working Group. J Cyst Fibros. 2015 Nov; 14(6): 706–713

(45) Daftary A, Acton J, Heubi J, Amin R. Fecal elastase-1: utility in pancreatic function in cystic fibrosis**.** J Cyst Fibros 2006;5(2):71-76.

(46) Loser C, Mollgaard A, Folsch U. Faecal elastase 1: a novel highly sensitive, and specific tubeless pancreatic function test . Gut 1996;39(4):580-586.

(47) Sharma G. Cystic Fibrosis Clinical Presentation. 2016; Available at: http://emedicine.medscape.com/article/1001602-clinical. Accessed December 2016.

(48) Ng M, Flight W, Smith E. Pulmonary complications of cystic fibrosis. Clin J Radiol 2014;69(3):153-162.

(49) Hamutcu R, Rowland J, Horn M, Kaminsky C, MacLaughlin E, Starnes V, et al. Clinical findings and lung pathology in children with cystic fibrosis. Am J Respir Criti Care Med 2002;165(8):1172-1175.

(50) Bradley J, Moran F, Elborn J. Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: an overview of five Cochrane systematic reviews. Respir Med 2006;100(2):191-201.

(51) Flume P, O'Sullivan B, Robinson K, Goss C, Mogayzel P, Willey-Courand D, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007;176(10):957-969.

(52) Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis. Cochrane Database Syst Rev. 2016

(53) Robinson M, Hemming A, Regnis J, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis Thorax 1997;52(10):900-903.

(54) Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, et al. A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis. N Engl J Med 2006 01/19; 2017/04;354(3):229-240.

(55) National Institute for Health and Care Excellence. Mannitol dry powder for inhalation for treating cystic fibrosis. 2012; Available at: https://www.nice.org.uk/Guidance/ta266. Accessed December 2016.

(56) BMJ Best Practice. Cystic fibrosis: Management approach. 2017 Available at: 2017, http://bestpractice.bmj.com/best-practice/monograph/403/treatment/step-by-step.html Accessed March 2017

(57) Hofer M, Benden C, Inci I, Schmid C, Irani S, Speich R, et al. True Survival Benefit of Lung Transplantation for Cystic Fibrosis Patients: The Zurich Experience. J Heart Lung Transplant 2009 4;28(4):334-339.

(58) Ntimbane T, Comte B, Mailhot G, Ntimbane T, Comte B, Mailhot G, et al. Cystic Fibrosis-Related Diabetes: From CFTR Dysfunction to Oxidative Stress. Clin Biochem Rev 2009;30(4):153-177.

(59) Tirosh A, Potashnik R, Bashan N, Rudich A. Oxidative stress disrupts insulin-induced cellular redistribution of insulin receptor substrate-1 and phosphatidylinositol 3-kinase in 3T3-L1 adipocytes. A putative cellular mechanism for impaired protein kinase B activation and GLUT4 translocation. J Biol Chem 1999;274:10595- 602.

(60) Nathan B, Moran A. Treatment recommendations for cystic fibrosis-related diabetes: too little, too late? Thorax 2011;66(7):555-556.

(61) Moran A, Brunzell C, Cohen R, Katz M, Marshall B, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33(12):2697-2708.

(62) Wang G, Gao C, Wei D, Wang C, Ding S. Acute pancreatitis: Etiology and common pathogenesis. World J Gastroenterol 2009;15(12):1427-1430.

(63) Colombo C, Russo M, Zazzeron L, Romano G. Liver disease in cystic fibrosis. Paediatr Gastroenterol Nutr 2006;43(1):49-55.

(64) Nutrition Consensus Working Group. Nutritional Management of Cystic Fibrosis. 2016.

(65) Borowitz D, Baker R, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Paediatr Gastroenterol Nutr 2002;35(3):246-259.

(66) Kobelska-Dubiel N, Klincewicz B, Cichy W. Liver disease in cystic fibrosis. *Przegląd Gastroenterologiczny*. 2014;9(3):136-141.

(67) Edenborough F. Women with cystic fibrosis and their potential for reproduction. Thorax 2001;56(8):649-655.

(68) Xu W, Shi Q, Chen W, Zhou C, Ni Y, Rowlands D, et al. Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. Proceedings of the National Academy of Sciences of the United States of America 2007;104(23):9816-9821.

(69) Blau H, Freud E, Mussaffi H, Werner M, Konen O, Rathaus V. Urogenital abnormalities in male children with cystic fibrosis. Arch Dis Child 2002;87:135-138.

(70) Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database of Syst Rev.

(71) Quittner A, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. Thorax 2014;69(12):1090-1097.

(72) Ernst M, Johnson M, Stark L. Developmental and psychosocial issues in CF. Child Adolesc Psychiatr Clin N Am. 2010;19(2):263-268.

(73) Bryon M, Shearer J, Davies H. Eating disorders and disturbance in children and adolescents with cystic fibrosis. Children's Health Care 2008;37(1):67-77.

(74) Cruz I, Marciel K, Quittner A, Schechter M. Anxiety and depression in cystic fibrosis. Semin Respir Crit Care Med 2009;30(5):569-578.

(75) Duff A, Abbott J, Cowperthwaite C, Sumner C, Hurley M, Quittner A. Depression and anxiety in adolescents and adults with cystic fibrosis in the UK: a cross sectional study. J Cyst Fibros 2014;13(6):745-753.

(76) MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of Patients With Cystic Fibrosis in 2000 to 2010 and Beyond: Survival Analysis of the Cystic Fibrosis Foundation Patient Registry. *Annals of internal medicine*. 2014;161(4):233-241.

(77) McKone E, Emerson S, Edwards K, Aitken M. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. Lancet 2003;361(9370):1671-1676.

(78) Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. Am J Epidemiol 1997;145(9):794-803.

(79) Hurley MN, McKeever TM, Prayle AP, Fogarty AW, Smyth AR. Rate of improvement of CF life expectancy exceeds that of general population—Observational death registration study. *Journal of Cystic Fibrosis*. 2014;13(4):410-415.

(80) McCarthy C, O'Carroll O, Franciosi A, McElvaney N. Factors Affecting Prognosis and Prediction of Outcome in Cystic Fibrosis Lung Disease. In: Wat D, editor. Cystic Fibrosis in the Light of New Research Rijeka, Croatia: InTech; 2015. Chapter 1.

(81) Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen H, Pressler T, Smyth R, et al. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. Thorax 2012;67(10):860-866.

(82) Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of Mortality in Patients with Cystic Fibrosis. N Engl J Med 1992 04/30; 2017/03;326(18):1187-1191.

(83) Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014;43(1):125-133.

(84) Belkin R, Henig N, Singer L, Chaparro C, Rubenstein R, Xie S, et al. Risk Factors for Death of Patients with Cystic Fibrosis Awaiting Lung Transplantation. Am J Respir Crit Care Med 2006;173(6):659-666.

(85) Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. N Engl J Med 2011 11/03; 2017/04;365(18):1663-1672.

(86) Murphy M, Caraher E. Current and Emerging Therapies for the Treatment of Cystic Fibrosis or Mitigation of Its Symptoms. Drugs in R&D 2016;16(1):1-17.

(87) Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordoñez CL, et al. Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del-CFTR Mutation. Chest 2012 9;142(3):718-724.

(88) US Food and Drug Administration,). Orkambi™ (lumacaftor/ivacaftor) [prescribing information] 2016; Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm505856.htm. Accessed February, 2017.

(89) Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015 07/16; 2017/04;373(3):220-231.

(90) Alton EWFW, Armstrong DK, Ashby D, Bayfield KJ, Bilton D, Bloomfield EV, et al. Repeated nebulisation of non-viral CFTR gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial. The Lancet Respir Med 2015 9;3(9):684-691.

(91) Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients J Cyst Fibros 2011;10(2):24-28.

(92) Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional Bowel Disorders. Gastroenterol 2017/04;130(5):1480-1491.

(93) Doef HP, Slieker MG, Staab D, et al. Association of the CLCA1 p.S357N variant with meconium ileus in European patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50:347–9. doi: 10.1097/MPG.0b013e3181afce6c.

(94) Rubinstein S, Moss R, Lewiston N. Constipation and meconium ileus equivalent in patients with cystic fibrosis. Pediatrics. 1986;78:473–9.

(95) Baker SS, Borowitz D, Duffy L, et al. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. J Pediatr. 2005;146:189–93. doi: 10.1016/j.jpeds.2004.09.003.

(96) Doef HP, Kokke FT, Beek FJ, et al. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. J Cyst Fibros. 2010;9:59–63. d

(97) Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol. 2006;41:35–49.

(98) Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros. 2002;1:51–75.

(99) Proesmans M, Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr. 2002;35:610–4

(100) Ali SR, Ahmed S, Qadir M, Humayun KN, Ahmad K. Fecal Incontinence and Constipation in Children: A Clinical Conundrum. *Oman Medical Journal*. 2011;26(5):376-378.

(101) National Institute for Healthcare and Excellence (NICE). Constipation in Children [Clinical knowledge summaries]. 2015; Available at: http://cks.nice.org.uk/constipation-in-children#!scenario. Accessed November, 2016.

(102) Houwen R, Van der Doef H, Sermet I, Munck A, Hauser B, Walkowiak J. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Paediatr Gastroenterol Nutr 2010;50(1):38-42.

(103) Borowitz, SM. Paediatric Constipation. 2017; Available at: http://emedicine.medscape.com/article/928185-overview?pa=uz%2Bu9oSrwFx%2FRmgplgqREKn1S0j8Ao2oGOrTqYwoV9agxXr8cYCNxxjBUmVKItCsz8SEBgudjkwffVinUcEpZiwhCTQq25Ki1mL6i64Z7Vg%3D Accessed July 2017.

(104) Joint Formulary Committee. British National Formulary (online). 2017; Available at: http://www.medicinescomplete.com. Accessed January, 2017.

(105) Jensen K. Meconium-ileus equivalent in a 15-year-old patient with mucoviscidosis.. Acta Paediatrica 1962;51:344-348.

(106) Lillibridge C, Docter J, Eidelman S. Oral administration of n-acetyl cysteine in the prophylaxis of "meconium ileus equivalent". J Paediatr 1967;71(6):887-889.

(107) O'Halloran S, Gilbert J, McKendrick O, Carty H, Heaf D. Gastrografin in acute meconium ileus equivalent. Arch Dis Child 1986;61(11):1128-1130.

(108) Cleghorn G, Forstner G, Stringer G, Durie P. Treatment of distal intestinal obstruction syndrome in cystic fibrosis with a balanced intestinal lavage solution. The Lancet 1986;327(8471):8-11.

(109) Davidson A, Harrison K, Steinfort C, Geddes D. Distal intestinal obstruction syndrome in cystic fibrosis treated by oral intestinal lavage, and a case of recurrent obstruction despite normal pancreatic function. Thorax 1987;42(7):538-541.

(110) Dray X, Bienvenu T, Desmazes-Dufeu N, Dusser D, Marteau P, Hubert D. Distal intestinal obstruction syndrome in adults with cystic fibrosis. Clin Gastroenterol Hepatol 2004;2(6):498-503.

(111) Munck A, Alberti C, Colombo C, Kashirskaya N, Ellemunter H, Fotoulaki M, et al. International prospective study of distal intestinal obstruction syndrome in cystic fibrosis: Associated factors and outcome. J Cyst Fibros 2016;15(4):531-9.

(112) Lavie M, Manovitz T, Vilozni D, Levy-Mendelovich S, Sarouk I, Weintraubv I. Long-term follow-up of distal intestinal obstruction syndrome in cystic fibrosis. World J Gastroenterol 2015;21(1):318-325.

(113) Hess D, MacIntyre N, Galvin W, Mishoe S, Volsko T, O'Malley C. Chapter 37: Cystic Fibrosis. Respiratory Care: Principles and Practice . 3rd ed.: Sudbury (MA): Jones and Bartlett Publishers Inc; 2015. p. 896.

(114) Bhalla V, Hallows K. Mechanisms of ENaC regulation and clinical implications. Clin J Am Soc Nephrol 2008;19(10):1845-1854.

(115) Taylor C, Hardcastle J. Gut Disease: Clinical manifestations, pathophysiology, current and new treatments. Bush A, Alton EWFW, Davies JC, Griesenbach U, Jaffe A (eds): Cystic Fibrosis in the 21st Century. Prog Respir Res. Basel, Karger, 2006, vol 34, pp 232-241

(116) De Lisle R, Borowitz D. The Cystic Fibrosis Intestine. Cold Spring Harb Perspect Med 2013;3(9).

(117) Garcia M, Yang N, Quinton P. Normal mouse intestinal mucus release requires cystic fibrosis transmembrane regulator-dependent bicarbonate secretion. J Clin Invest 2009;119(9):2613-2622.

(118) Verdugo P. Supramolecular dynamics of mucus. Cold Spring Harb Perspect Med 2012;2(11).

(119) Rosenstein B, Langbaum T. Incidence of distal ileal obstruction syndrome in cystic fibrosis. J Paediatr Gastroenterol Nutr 1983;2(2):299-301.

(120) Smith V, Schäppi M, Bisset W, Kiparissi F, Jaffe A, Milla P, et al. Lymphocytic leiomyositis and myenteric ganglionitis are intrinsic features of cystic fibrosis: studies in distal intestinal obstruction syndrome and meconium ileus. J Paediatr Gastroenterol Nutr 2009;49(1):42-51.

(121) Dialer I, Hundt C, Bertele-Harms R, Harms H. Sonographic evidence of bowe wall thickness in patients with cystic fibrosis. J Clin Gastroenterol 2003;37(1):55-60.

(122) Shidrawi R, Murugan N, Westaby D, Gyi K, Hodson M. Emergency colonoscopy for distal intestinal obstruction syndrome in cystic fibrosis patients.Gut 2002;51(2):285-286.

(123) Agrons G, Corse W, Markowitz R, Suarez E, Perry D. Gastrointestinal manifestations of cystic fibrosis: radiologic-pathologic correlation. Radiographics 1996;16(4):871-893.

(124) Robertson MB, Choe KA, Joseph PM. Review of the Abdominal Manifestations of Cystic Fibrosis in the Adult Patient. Radiographics 2006 05/01; 2017/02;26(3):679-690.

(125) Tuladhar R, Daftary A, Patole S, Whitehall J. Oral gastrografin in neonates: a note of caution. Int J Clin Pract 1999;53(7):565.

(126) (22) Shah HM CK. Archie Cochrane and his vision for evidence-based medicine. Plastic and reconstructive surgery 2009;124(3):982-988.

(127) The Cochrane Collaboration. What is Cochrane evidence and how can it help you? 2017; Available at: http://www.cochrane.org/what-is-cochrane-evidence. Accessed May 2017.

(128) Hodson M, Bush A, Geddes D. Gastrointestinal disease in cystic fibrosis. Cystic Fibrosis. 3rd Edition. Boca Raton (FA): In: Hodson M, Bush A, Geddes D, editors. Cystic Fibrosis. 3rd ed.: CRC Press; 2012. p. 216-217.

(129) Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. 5.1st ed.: The Cochrane Collaboration; March 2011.

(130) Light R, Pillemer D. *Summing Up. The Science of Reviewing Research.* 1st ed. Cambridge: Harvard University Press; 1984.

(131) The Cochrane Collaboration. Review Manager (RevMan) 2014;5.3.

(132) The Cochrane Collaboration. About RevMan 5. 2017; Available at: http://community.cochrane.org/tools/review-production-tools/revman-5/about-revman-5. Accessed May 2017.

(133) Altman D, Bland J. Time to event (survival) data. BMJ 1998;317(7156):468-468.

(134) Ryan R, Hill S, Broclain D, Horey D, Oliver S, Prictor M. Cochrane Consumers and Communication Review Group. Study Design Guide. June 2013; Available at: http://cccrg.cochrane.org/author-resources. Accessed May 2017.

(135) Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL). 2017; Available at: http://onlinelibrary.wiley.com/cochranelibrary/search?searchRow.searchOptions.searchProducts=clinicalTrialsDoi. Accessed April, 2017.

(136) Ovid Technologies Inc. Ovid MEDLINE®. 2017; Available at: https://openathens.ovid.com/secure-ssl/discovery.jsp. Accessed April, 2017.

(137) National Institute for Healthcare and Excellence (NICE). Embase: Healthcare Databases Advanced Search. 2017; Available at: https://hdas.nice.org.uk/. Accessed April, 2017.

(138) The Cochrane Collaboration. Cystic Fibrosis and Genetic Disorders Group. 2017; Available at: http://cfgd.cochrane.org/our-specialised-trials-registers. Accessed April, 2017.

(139) ClinicalTrials.gov. 2017; Available at: https://clinicaltrials.gov/ct2/home. Accessed April, 2017.

(140) ISRCTN Registry. 2017; Available at: https://www.isrctn.com/. Accessed April, 2017.

(141) World Health Organisation (WHO). International Clinical Trials Registry Platform Search Portal. 2017; Available at: http://apps.who.int/trialsearch/. Accessed April, 2017.

(142) OpenGrey search portal. 2017; Available at: http://www.opengrey.eu/search/. Accessed April, 2017.

(143) The Cochrane Collaboration. Cochrane Methods: MECIR. 2017; Available at: http://methods.cochrane.org/mecir. Accessed April, 2017.

(144) Database Search Tips: Boolean Operators. Available at: http://libguides.mit.edu/c.php?g=175963&p=1158594. Accessed April, 2017.

(145) Veritas Health Innovation. Covidence systematic review software. Covidence ;2017.

(146) Meade M, Richardson W. Selecting and appraising studies for a systematic review. Ann Intern Med 1997;127:531-537.

(147) Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 ed. The Cochrane Collaboration, 2011; 2011.

(148) Deeks J, Higgins J, Altman D. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [updated March 2011] ed.: The Cochrane Collaboration; 2011.

(149) Higgins J, Deeks J, Altman D. Chapter 16: Special topics in statistics. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [upated March 2011] ed.: The Cochrane Collaboration; 2011.

(150) Higgins J, Deeks J. Chapter 7: Selecting studies and collecting data. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [updated March 2011] ed.: The Cochrane Collaboration; 2011.

(151) Elbourne D, Altman D, Higgins J, Curtin F, Worthington H, Vail A. Meta-analyses involving cross-over trials: methodological issues Int J Epidemiol 2002;31(1):140-149.

(152) Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990;263(10):1385-1389.

(153) Sterne J, Egger M, Moher D. Chapter 10: Adressing reporting biases. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [updated March 2011] ed.: The Cochrane Collaboration; 2011.

(154) Stewart L, Tierney J, Clarke M. Chapter 18: Reviews of Individual Patient Data. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [updated March 2011] ed.: The Cochrane Collaboration; 2011.

(155) Schunemann H, Fretheim A, Oxman A. Improving the use of research evidence in guideline development: 13. Applicability, transferability and adaptation Health Res Policy Syst 2006;4:25.

(156) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

(157) Koletzko S, Corey M, Ellis L, Spino M, Stringer DA, Durie PR. Effects of cisapride in patients with cystic fibrosis and distal intestinal obstruction syndrome. J Pediatr 1990;117(5):815-822.

(158) Dietzsch H.J., Berger G., Gottschalk B. Results of oral acetylcysteine therapy in children with cystic fibrosis. Eur J Respir Dis 1980;61:135.

(159) Gotz M, Kraemer R, Kerrebijn KF, Popow C. Oral acetylcysteine in cystic fibrosis. A co-operative study. European Journal of Respiratory Diseases - Supplement 1980;111:122-126.

(160) Howatt WF, DeMuth GR. A double-blind study of the use of acetylcysteine in patients with cystic fibrosis. Univ Mich Med Cent J 1966;32(2):82-85.

(161) Baran D. Mucolytic treatment in cystic fibrosis. Double-blind clinical trial with oral acetylcysteine and placebo. Eur J Respir Dis 1980;61:134.

(162) Mitchell EA, Elliott RB. Failure of oral N-acetylcysteine to improve the malabsorption of cystic fibrosis. Aust Paediatr J 1981;17(3):207-208.

(163) Dalzell AM, Heaf DP. High dose pancreatic enzymes in distal intestinal obstruction syndrome abstract. Paediatric Research Society Meeting 1992:148

(164) O'Brien CE, Anderson PJ, Stowe CD. Lubiprostone for constipation in adults with cystic fibrosis: a pilot study. Ann Pharmacother 2011;45(9):1061-1066.

(165) Chen J, Ou L, Hollis S. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 2013;13:211.

(166) GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490-1494.

(167) Ferriman A. UK licence for cisapride suspended. BMJ. 2000;321(7256):259.

(168) Qualtrics: Online Survey Software and Insight Platform. 2017; Available at: https://www.qualtrics.com/. Accessed February, 2017, 2017.

(169) STATA Corp, College Station, Texas, USA

Chapter 11: Appendices

Appendix 1: Search strategies for the databases used in the Cochrane systematic review.

This appendix contains the search strategies for CENTRAL, MEDLINE, EMBASE, clinicaltrials.gov, ISRCTN registry, WHO ICTRP and OpenGrey.

CENTRAL

#1 Cystic Fibrosis *[MeSH descriptor]*
#2 cystic fibrosis:ti,ab
#3 fibrocystic near/10 disease near/10 pancreas
#4 mucoviscidos*:ti,ab
#5 cystic* near/10 fibros*:ti,ab
#6 #1 or #2 or #3 or #4 or #5
#7 distal intestinal obstruction syndrome*:ti,ab
#8 dios or mie:ti,ab
#9 Intestinal Obstruction *[MeSH descriptor]*
#10 meconium ileus equivalent:ti,ab
#11 faecal near/3 (obstruction or impact*):ti,ab
#12 Constipation *[MeSH descriptor]*
#13 constipat*:ti,ab
#14 laxative*:ti,ab
#15 Laxatives *[MeSH descriptor]*
#16 lactulose:ti,ab
#17 Lactulose *[MeSH descriptor]*
#18 (macrogol or polyethylene glycol*):ti,ab
#19 Polyethylene Glycols *[MeSH descriptor]*
#20 movicol:ti,ab
#21 klean*:ti,ab
#22 diatriozate:ti,ab
#23 gastrografin:ti,ab
#24 sennati:ti,ab
#25 docusate:ti,ab
#26 picosulfate:ti,ab
#27 acetylcysteine or fibrol:ti,ab
#28 parvolex:ti,ab
#29 fibre:ti,ab
#30 picosulphate:ti,ab
#31 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 #30
#32 #6 and #31

MEDLINE Ovid (1946 onwards)

1. Cystic Fibrosis/
2. cystic fibrosis.tw.

3. (fibrocystic adj10 disease adj10 pancreas).tw.
4. mucoviscidos$.tw.
5. (cystic$ adj10 fibros$).tw.
6. 1 or 2 or 3 or 4 or 5
7. "distal intestinal obstruction syndrome*".tw.
8. (dios or mie).tw.
9. Intestinal Obstruction/
10. meconium ileus equivalent.tw.
11. (faecal adj3 (obstruction or impact*)).tw.
12. Constipation/
13. "constipat*".tw.
14. "laxative*".tw.
15. Laxatives/
16. lactulose.tw. or Lactulose/
17. (macrogol or polyethylene glycol*).tw. or Polyethylene Glycols/
18. movicol.tw.
19. klean*.tw.
20. diatriozate.tw.
21. gastrografin.tw.
22. senna.tw.
23. docusate.tw.
24. picosulfate.tw.
25. acetylcysteine or fibrol.tw.
26. parvolex.tw.
27. fibre.tw.
28. picosulphate.tw.
29. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 6 and 29

Embase Ovid (1974 onwards)

1. CYSTIC FIBROSIS/
2. cystic fibrosis.tw.
3. (fibrocystic adj10 disease adj10 pancreas).tw.
4. mucoviscidos$.tw.
5. (cystic$ adj10 fibros$).tw.
6. 1 or 2 or 3 or 4 or 5
7. "distal intestinal obstruction syndrome*".tw.
8. (dios or mie).tw.
9. INTESTINE OBSTRUCTION/
10. meconium ileus equivalent.tw.
11. (faecal adj3 (obstruction or impact*)).tw.
12. CONSTIPATION/
13. "constipat*".tw.
14. "laxative*".tw.
15. LAXATIVE/
16. lactulose.tw. or LACTULOSE/
17. (macrogol or polyethylene glycol*).mp,hw.
18. movicol.tw.
19. klean*.tw.

20. diatriozate.tw.
21. gastrografin.tw.
22. senna.tw.
23. docusate.tw.
24. picosulfate.tw.
25. acetylcysteine or fibrol.tw.
26. parvolex.tw.
27. fibre.tw.
28. picosulphate.tw.
29. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 6 and 29

Clinicaltrials.gov

ADVANCED SEARCH

Search 1
Search terms: laxative OR laxatives OR lactulose OR macrogol OR polyethylene OR movicol OR klean OR diatriozate OR gastrografin OR senna OR docusate OR picosulfate OR acetylcysteine OR fibrol OR parvolex OR picosulphate OR fibre
Study type: Interventional Studies
Conditions: cystic fibrosis

Search 2
Search terms: intestinal OR DIOS OR constipation OR constipated OR faecal OR meconium
Study type: Interventional Studies
Conditions: cystic fibrosis

ISRCTN Registry

ADVANCED SEARCH
Condition: cystic fibrosis

WHO ICTRP

BASIC SEARCHES

Search 1: cystic fibrosis AND intestinal
Search 2: cystic fibrosis AND constipation
Search 3: cystic fibrosis AND faecal
Search 4: cystic fibrosis AND meconium
Search 5: mucoviscidose

ADVANCED SEARCH

Condition: cystic fibrosis
Intervention: laxative OR laxatives OR lactulose OR macrogol OR polyethylene OR movicol OR klean OR diatriozate OR gastrografin OR senna OR docusate OR picosulfate OR acetylcysteine

OR fibrol OR parvolex OR picosulphate OR fibre *Recruitment Status:* All
Open Grey (cystic fibrosis OR cf OR mucoviscidos*) AND (intestin* OR constipat* OR faecal OR meconium OR laxative* OR lactulose OR macrogol OR polyethylene OR movicol OR klean* OR diatriozate OR gastrografin OR senna OR docusate OR picosulfate OR acetylcysteine OR fibrol OR parvolex OR picosulphate OR fibre)

Appendix 2: Protocol for the Interventions for Preventing Distal Intestinal Obstruction Syndrome in Cystic Fibrosis.

This protocol can also be accessed online at:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012619/full

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis (Protocol)

Green J, Carroll W, Gilchrist FJ

Green J, Carroll W, Gilchrist FJ.
Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012619.
DOI: 10.1002/14651858.CD012619.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

Jessica Green[1], Will Carroll[2], Francis J Gilchrist[1]

[1]Academic Department of Child Health, Royal Stoke University Hospital, Stoke-on-Trent, UK. [2]Department of Paediatric Respiratory Medicine, University Hospitals of the North Midlands, Stoke-on-Trent, UK

Contact address: Will Carroll, Department of Paediatric Respiratory Medicine, University Hospitals of the North Midlands, Newcastle Road, Stoke-on-Trent, ST4 6QG, UK. will.carroll@nhs.net.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Green J, Carroll W, Gilchrist FJ. Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012619. DOI: 10.1002/14651858.CD012619.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This review aims to evaluate the effectiveness and safety of laxative agents of differing types for preventing DIOS (complete and incomplete) in children and adults with CF. If possible, we aim to assess the optimal laxative regimen by comparing the evidence for osmotic laxatives, stimulant laxatives and mucolytic agents.

BACKGROUND

Cystic fibrosis (CF) is an important genetic disorder. It is life-limiting and affected individuals have dysfunction of several organ systems which results in morbidity and reduced quality of life (QoL). To be affected a person must possess two faulty copies of the gene that encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). About 1 in 25 of the UK white population carry a single faulty copy of this gene and one in 2500 newborns in the UK are born with CF (Tobias 2011). Worldwide the condition affects approximately 70,000 children and adults (CF Foundation 2016).

Although respiratory symptoms are prominent, and often the focus of clinical care, CF is a multifaceted disease which also has important effects on the gastrointestinal and endocrine systems. The CFTR is expressed in many cell types throughout the body; it regulates chloride transport and thus indirectly influences water transport across the cell membranes. Absent or dysfunctional CFTR leads to thickened, dehydrated mucus.

Description of the condition

Intestinal obstruction in CF

Distal intestinal obstruction syndrome (DIOS) is a well-recognised morbidity in CF. It is the result of the accumulation of thick and sticky material within the bowel (both mucus and faeces) particularly in the final part of the small intestine (the terminal ileum and caecum). This mass becomes connected to the bowel wall itself and the finger-like projections of the small bowel (intestinal villi) making it fixed in position and difficult to remove (Colombo 2011). The bowel may be completely blocked (complete DIOS) or only partially blocked (incomplete DIOS), e.g. when a persis-

tent mass is found low down on the right-hand side (right iliac fossa). Previously DIOS was known as meconium ileus equivalent (MIE), and affects between 10% to 22% of individuals with CF (Davidson 1987; Dray 2004; Penketh 1987; Rubinstein 1986). The reported incidence increases with age, with almost 80% of new cases occurring in adults (Dray 2004). Once an individual has had DIOS the recurrence risk is about 50% (Dray 2004). A number of factors contribute to the occurrence of DIOS. It occurs more commonly in individuals who have pancreatic enzyme deficiency (Munck 2016) and anecdotally is more common in those who do not adhere to pancreatic enzyme replacement therapy. In part, it occurs due to the loss of CFTR function in the intestine, where CFTR regulates chloride, bicarbonate and sodium transport.

Distinguishing DIOS from other causes of bowel obstruction in CF

The CF gut is prone to obstruction from other causes due to its altered pathophysiology (van der Doef 2011). A small but significant proportion of newborns with CF present either at birth or shortly afterwards with bowel obstruction - meconium ileus. Meconium ileus occurs in 13% to 17% of the CF population (van der Doef 2011). Throughout life, children and adults with CF are prone to constipation, with almost half of all children studied (47%) having evidence of constipation (van der Doef 2010). However, it is possible to distinguish between constipation and DIOS both clinically and radiologically. One widely-used definition of DIOS is an acute complete or incomplete faecal obstruction in the ileocecum; whereas constipation is defined as gradual faecal impaction of the total colon (Houwen 2010). Using this definition in individuals under 18 years of age, 51 episodes of DIOS in 39 individuals were recorded, giving an overall incidence of 6.2 (95% confidence interval (CI) 4.4 to 7.9) episodes per 1000 patient-years. Although there is undoubtedly overlap between constipation and incomplete DIOS, the clinical definition proposed by Houwen permits the effectiveness of treatments to be monitored clinically (Houwen 2010).

Description of the intervention

Treatment of constipation and the prevention of complete bowel obstruction is required as part of optimal care for individuals with CF. DIOS is predominantly an ileocaecal pathology (Houwen 2010). Many strategies are currently used in clinical practice and there is a lack of consensus about what the best preventative measures are likely to be. In addition to ensuring adequate hydration and adherence with pancreatic enzyme supplementation, different centres use different combinations of laxatives to prevent DIOS including lactulose, senna, polyethylene glycol (e.g. Movicol®), sodium docusate, sodium picosulphate and fibre.

Although most children and adults with CF are prescribed interventions to prevent DIOS at some stage, there is significant heterogeneity observed between clinicians in their choices of agent. With the advent of newer laxative agents, e.g. Movicol®, some centres have changed their approach.

This review will focus upon the use of laxative agents (aperients) for the prevention of DIOS. There are three main groups of laxatives based upon their primary mechanism of action (although there is overlap between the mechanism of action for some agents).

1. Osmotic laxatives

Osmotic laxatives are faecal softeners which work by increasing water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with.

Lactulose

Lactulose is given orally; it is widely used, but may cause flatulence or abdominal pain in high doses (Colombo 2011).

Macrogol 3350

Macrogol 3350 is also known as polyethylene glycol, or under the brand names Movicol®, Laxido® or Klean-Prep®. Movicol® is recommended as first-line treatment for constipation (NICE 2015). It is commonly given to children for chronic constipation or at a higher dose in faecal impaction. It can be given as an oral solution or powder (BNFc 2016). Laxido® is a very similar product which is also recommended for treatment of chronic constipation or impaction. Klean-Prep® can also be used, with the aim to cleanse the bowel. The solution is given until clear fluid is passed per rectum. As larger volumes are required, it is often necessary to administer via gastrostomy or nasogastric tube (Colombo 2011; NICE 2015).

Diatrizoate

Oral diatrizoate (also known as Gastrografin®) is used by many centres to treat DIOS. It is given as a single dose, which can be repeated after 24 hours. Rectal diatrizoate can also be used in more severe cases (Colombo 2011). As diatrizoate is highly osmotic, the individual must be adequately hydrated prior to administration in order to avoid complications such as shock and perforation of the bowel (Tuldahar 1999).

2. Stimulant laxatives

Senna

Senna acts by stimulating peristalsis and increases the emptying of the bowel. Senna is therefore useful when the individual has soft stools, but finds it difficult to pass them (NICE 2015).

Sodium docusate

Sodium docusate acts both as a stimulant and also as a stool softener. It can be administered orally, but if this does not relieve faecal impaction, the drug can also be given as an enema (NICE 2015).

Sodium picosulphate

Sodium picosulphate acts by stimulating the mucosa of the large bowel, increasing its motility; it is given as an oral solution (BNFc 2016).

3. Mucolytics

Oral N-acetylcysteine

N-acetylcysteine (also known as Parvolex®) is indicated for abnormal or impaired mucus production. It can be given as a single oral dose for treatment of meconium ileus or DIOS. It is typically diluted in a sweet drink, such as orange juice or cola, to mask the strong and bitter taste (BNFc 2016).

How the intervention might work

Different aperients have different mechanisms of action. Historically these have been divided into three broad categories as stated above. In clinical practice it has been helpful to titrate the doses of these to achieve a reduction in abdominal pains and a normal physical examination, e.g. resolution of right iliac fossa mass. Some newer agents (e.g. Movicol®) combine these effects providing both softening and stimulation.

For preventing DIOS, laxatives are likely to work by increasing stool volume and reducing gut transit time or by softening mucofaeculant material that has built up in the gut. The passage of larger volumes of more liquid stool may have a mechanical effect on any adherent mucofaeces. However, the use of high doses of laxatives are likely to lead to other undesirable consequences including the unacceptable frequency of stooling, soiling, abdominal distension, flatulence and abdominal pain.

Why it is important to do this review

Intestinal obstruction is an important and common problem in CF. Incomplete DIOS is relatively common and there is considerable variation in practice. In our clinical experience, prophylaxis for DIOS is given to individuals who have had an episode of complete DIOS, those who have clinical signs consistent with incomplete DIOS or those with pancreatic insufficiency and clinical or radiological manifestations of constipation (e.g. faecal masses palpable on clinical examination or reported abdominal pain). The evidence base for this practice is unclear and there is no clear evidence base for any preventative therapies for DIOS (Colombo 2011).

Individuals with CF undergo a very large treatment burden. In discussing the risks and benefits of preventative treatment for DIOS it is important that we give clear information about the likely side effects and tolerability of any proposed therapy.

OBJECTIVES

This review aims to evaluate the effectiveness and safety of laxative agents of differing types for preventing DIOS (complete and incomplete) in children and adults with CF. If possible, we aim to assess the optimal laxative regimen by comparing the evidence for osmotic laxatives, stimulant laxatives and mucolytic agents.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised-controlled trials (RCT) and quasi-RCTs. We will assess quasi-RCTs on their merit using the Cochrane risk of bias tool and if both reviewers are satisfied that the groups were similar at baseline, we will include them.

We will also assess cross-over trials for possible inclusion on an individual basis. If we deem the treatment to alter the condition to the extent that, on entry to subsequent phases, the participants differ from their initial state, we will exclude the trial unless we can use data from the first phase only (see Unit of analysis issues).

Types of participants

Children and adults with CF diagnosed by sweat test or genetic testing, with all stages and severity of lung disease and with or without pancreatic sufficiency.

Types of interventions

We will compare the different treatment groups of enteral laxative therapy for preventing DIOS (including osmotic agents, stimulants, mucolytics and substances which have more than one action) at any dose to placebo, no treatment or an alternative oral laxative therapy.

As some treatments have significant overlap in their mechanisms of action (e.g. Movicol® is a osmotic agent which also has a stimulant effect), it is proposed that initial analysis will attempt to examine whether any preventative treatment is effective. The relative effectiveness of different classes of agents will be examined as a subgroup analysis.

Types of outcome measures

Primary outcomes

1. Complete or incomplete DIOS diagnosed either clinically (e.g. abdominal masses, or distension or pain) or radiologically (e.g. dilated bowel or faecal mass).
2. Adverse effects from treatments
   i) serious adverse effects of treatment regimens (including, but not limited to, rectal bleeding, intestinal perforation, mucosal erosions, anaphylactic reaction, vomiting with electrolyte disturbance)
   ii) other adverse effects of treatment (e.g. diarrhoea or soiling, abdominal distension, loss of continence or pain)

Secondary outcomes

1. Time to hospital admission
   i) all causes
   ii) due to DIOS
2. Patient-reported quality of life (QoL) scores
3. Patient-reported symptom scores
4. Tolerability (participant- or investigator-reported rates of concordance)

Search methods for identification of studies

Electronic searches

We will identify relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: distal intestinal obstruction syndrome [DIOS]. There will be no restrictions regarding language or publication status.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group website.

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library www.thecochranelibrary.com;
- MEDLINE Ovid (1946 onwards);
- Embase Ovid (1974 onwards).

We will also search the following trials registries and other resources:

- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
- International Standard Randomised Controlled Trial Number (ISRCTN) Registry (www.isrctn.com);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch);
- Open Grey (www.opengrey.eu/).

For details of our search strategies, please see the appendices (Appendix 1).

Searching other resources

We will check the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials.

Data collection and analysis

Selection of studies

Once we have the complete list of identified references, one author (WC) will check for and remove any duplicates. Two authors (WC and JG) will then review all titles and abstracts and discard references which clearly do not meet the inclusion criteria. We will attempt to resolve any disagreements by discussion, but if we can not reach a decision, we will ask the third author (FG) of the review to mediate until we can reach a final decision. Once we have discarded trials on the basis of title and abstract, we will obtain full copies of the remaining references and screen these using a standardised screening form customised for this review.

We will consider trials in any language and will translate them as necessary. We will include trials published as full texts, but if where there is only an abstract available, we will include it if it presents results. If there are no results presented within the abstract or on

any trials registry sites, then we will classify the trial as 'Awaiting assessment' until more information is available. Similarly with unpublished trials, if a trial meets our inclusion criteria and quality assessment then we will include it.
We will present the results of the search using a standardised flow chart.

Data extraction and management

Two authors (WC and JG) will independently extract data using a specially designed data extraction form developed by the Cochrane Cystic Fibrosis and Genetic Disorders Review Group and adapted to this review. We will collect data on:

- participant characteristics;
- trial characteristics and trial design;
- intervention and comparator;
- outcome data - we will report data for each outcome separately.

One author (WC) will check the independent data extraction forms for discrepancies and if there are any which we can not resolve by discussion, a third author (FG) will arbitrate.
We will enter the extracted data into the Review Manager software for analysis (RevMan 2014). We initially will carry out the a comparison of any laxative agent versus placebo or usual treatment and then, if possible, undertake subgroup analysis by type of laxative (see Subgroup analysis and investigation of heterogeneity).

Assessment of risk of bias in included studies

We will use the risk of bias tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias across six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias) (Higgins 2011).
If the trial describes the methods of randomisation and allocation, including the concealment of the allocation sequence from the researchers, and we deem these to be adequate, then we will rank the trial as having a low risk of bias for this domain. Where these are inadequate, we will rank the trial as being at a high risk and where it is unclear from the description given, then we will rank it as having an unclear risk of bias.
Similarly for blinding, we will look at the method used and who was blinded to determine the risk of bias.
We will extract information on missing data and how the investigators recorded participant withdrawals and loss to follow up. We will also look at whether missing data were equally distributed between the intervention and control groups. If all review authors agree that missing data have been accounted for adequately, then we will judge the trial to be at a low risk of bias. We will record the trial as having a high risk of bias if the missing data have not been reported adequately and will record it as having an unclear risk of bias if we are unable to see how the missing data have been reported. Two authors will assess each included trial to determine whether the investigators used an intention-to-treat (ITT) analysis and again, once we have reached an agreement, we will rank the trials as being at a high, low or unclear risk of bias.
If the trial investigators report all outcomes in the paper, the review authors will record a low risk of bias from selective reporting. If the paper states that investigators measured outcomes, but they do not report the results of these, the review authors will rank the paper as being at high risk. If it is unclear to the review authors whether the trial reports all outcomes measured, then we will state this and rank it as unclear for this domain. We will search for trial protocols to be able to assess outcome reporting. If we can not locate the protocol, we will assess outcome reporting based on a comparison between the methods section of the full published paper and the results section.
The review authors will look for any other potential sources of bias in the included trials and will record what they find. If neither author can find any other source of bias, then we will rank the trial as having a low risk for this domain and high risk if the opposite is true.
We will present the results of the risk of bias assessment both individually and in a summary table.

Measures of treatment effect

For dichotomous data (complete DIOS, incomplete DIOS, pooled adverse effects, failure to tolerate treatment and adherence), we will calculate a pooled estimate of the treatment effects for each outcome across trials using the risk ratio (RR) and 95% confidence intervals (CIs) where appropriate. For individual adverse events, e.g. reported soiling, then 99% CIs will be reported.
For continuous data (patient-reported QoL, symptom scores) we plan to record the mean change and standard deviation (SD) from baseline for each group. We intend to calculate a pooled estimate of treatment effect using the mean difference (MD) and 95% CIs. Where trials use different units of measurement or measurement scales for reporting the same outcome (which is likely to be true for QoL and symptom scores) we will use the standardised mean difference (SMD) to report the results. Where trials only report only a pre-intervention mean (SD) and post-intervention mean (SD) then we can calculate the mean change but not the SD of the change. We will report these results narratively.
For time-to-event data (e.g. time to hospitalisation) we will express the intervention effect as a hazard ratio (HR) with 95% CIs using the generic inverse variance method.
Where end-points are semantically different but report to similar outcomes then we will group outcomes. Thus, synonymous terms will be considered jointly. We will consider:

- abdominal distension (reported) to be synonymous with bloating, swelling or gaseous distension;
- pain to be synonymous with discomfort or ache;
- vomiting to be synonymous with emesis;

- constipation to be synonymous with straining or dyschezia.

Unit of analysis issues

We will assess any trials using a cross-over design to establish how much data we can include in the analysis. Where the authors have taken account of the cross-over design in the analysis, any carry-over effect and within-person differences, we will be able to include the trial. Where the data have not been analysed appropriately, we may be able to include data from the first phase of the cross-over trial as if it were a parallel design; although the advantage of the cross-over design (using participants as their own controls) would be lost (Elbourne 2002).

If we find trials which are multi-arm they will possibly fall into more than one comparison. In such cases, where the two active treatment arms are different types of laxative regimen, e.g. Movicol® versus lactulose and senna versus placebo, each treatment arm will be analysed separately against placebo and where appropriate included in a meta-analysis. If the two active treatment arms are of the same type of laxative (e.g. softening agents), but employ a different laxative or dose, we will combine them against the placebo arm to look at the effect of the type of laxative rather than an individual drug.

If there is heterogeneity between trials looking at different types of laxative regimen, we will carry out a subgroup analysis to look at the effect of individual drugs (Subgroup analysis and investigation of heterogeneity).

Dealing with missing data

We will attempt to request additional data from the trial author(s) if there are insufficient data in the published paper or uncertainty about data we are able to extract from the included trials. We will undertake an ITT analysis wherever possible throughout the review.

We will also assess the extent to which trial authors have employed an ITT analysis and we will report the numbers of participants who dropped out of each arm of the trial, where possible.

Where data is incomplete but partially available we will use the last available measurement to determine effectiveness.

Assessment of heterogeneity

Where there are trials reporting the same outcomes which we are able to include in a meta-analysis, we will assess the level of heterogeneity using the I^2 statistic. We will look at the overlap of the CIs on the forest plots to gauge the significance of the I^2 value. We will base our definitions of different levels of heterogeneity on the levels described in the *Cochrane Handbook for Systematic Reviews of Interventions*:

- low (might not be important) - 0% to 40%;
- moderate - 30% to 60%;
- substantial - 50% to 90%; and
- considerable - 75% to 100%.

The *Cochrane Handbook for Systematic Reviews of Interventions* states that this is a rough guide because the importance of inconsistency depends on several factors (Deeks 2011).

Assessment of reporting biases

Where we are able to include at least 10 trials, we will generate a funnel plot to attempt to identify any publication bias in the included trials (Sterne 2011). We will also attempt to identify any selective reporting in the included publications, by comparing the trial protocols with the final papers and by careful examination of the trial publications and consideration of reporting of both positive and negative effects of the intervention. Where trial protocols are not available, we will compare the outcomes reported in the results section against the methods section of the paper. We will extract information on the sponsors, sources of funding and competing interests of the authors to determine the role of external bias being introduced. To minimise publication bias, we will search trial registries and contact pharmaceutical companies for unpublished data.

Data synthesis

Where we are able to combine trials in a meta-analysis, we will use the data from the selected trials to generate forest plots using the Review Manager software (RevMan 2014). We plan to carry out an initial combined analysis of all types of laxative agent) followed by separate meta-analyses for different groups of laxative agents (e.g. osmotic laxatives, stimulants and those with a combined mechanism of action) and mucolytics. We will examine the level of heterogeneity to determine which type of analysis model to use. If there is low heterogeneity (less than 40%) then we will use a fixed-effect model and if the I^2 statistic is greater than 40% then we will use a random-effects model to summarize the data.

Subgroup analysis and investigation of heterogeneity

If there is greater than 40% heterogeneity among the included trials, we will undertake subgroup analyses to look at the following:

- children (18 years and under) versus adults;
- type of laxative (osmotic agent (e.g. lactulose) versus stimulant laxative regimes (e.g. senna) versus mucolytic (e.g. N-acetylcysteine));
- single regimens versus combined regimens (e.g. lactulose and senna)
- effectiveness of regimen in preventing complete versus incomplete DIOS* (Houwen 2010)

*The following definitions of complete and incomplete DIOS are taken from (Houwen 2010).

1. Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography.
2. Faecal mass in ileo-caecum.
3. Abdominal pain or distension (or both).

Complete DIOS is defined as when all three of the above criteria are present, whereas incomplete or impending DIOS is defined as only the second and third criteria being present.

Sensitivity analysis

Where we have performed a meta-analysis, we will carry out sensitivity analyses to look at the effect of the risk of bias findings. We will look at the effect of adding in and taking out trials where there is high risk of bias. We will also attempt to examine the effect of cross-over trials on the results by carrying out a sensitivity analysis to include and exclude them.

Summary of findings table

We will report summary of findings information, with a separate table for each treatment comparison, for our chosen outcomes comparing laxative agents versus control, placebo or alternate regimens for the outcomes: prevention of complete or incomplete DIOS, adverse events, hospitalisation for any cause, hospitalisation for DIOS, QoL, symptom score, and tolerability. Where no data for individual outcomes are available then a row in the table will identify this by entry of the notation: 'data not reported'.
For each outcome we will report the illustrative risk with and without the intervention, magnitude of effect (RR or MD), numbers of trials and participants addressing each outcome and a grade of the overall quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) with comments (Schunemann 2006).

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

Additional references

BNFc 2016
Joint Formulary Committee. London: BMJ Group and Pharmaceutical Press, 2016. *British National Formulary for Children*. Vol. **72**, London: BMJ Group and Pharmaceutical Press, 2016.

CF Foundation 2016
CF Foundation. About Cystic Fibrosis. www.cff.org/What-is-CF/About-Cystic-Fibrosis/ (accessed 13 April 2016).

Colombo 2011
Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, ECFS. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *Journal of Cystic Fibrosis* 2011;**10 Suppl 2**:S24–8. [DOI: 10.1016/S1569-1993(11)60005-2]

Davidson 1987
Davidson AC, Harrison K, Steinfort CL, Geddes DM. Distal intestinal obstruction syndrome in cystic fibrosis treated by oral intestinal lavage, and a case of recurrent obstruction despite normal pancreatic function. *Thorax* 1987;**42**(7):538–41.

Deeks 2011
Deeks J, Higgins J, Altman D, on behalf of the Cochrane Statistical Methods Group, editor(s). Chapter 9 Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from cochrane-handbook.org.

Dray 2004
Dray X, Bienvenu T, Desmazes-Dufeu N, Dusser D, Marteau P, Hubert D. Distal intestinal obstruction syndrome in adults with cystic fibrosis. *Clinical Gastroenterology and Hepatology* 2004;**2**(6):498–503.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from cochrane-handbook.org.

Houwen 2010
Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. *Journal of Paediatric*

Gastroenterology and Nutrition 2010;**50**(1):38–42. [DOI: 10.1097/MPG.0b013e3181a6e01d]

Munck 2016
Munck A, Corinne A, Colombo C, Kashirskaya N, Ellemunter H, Fotoulaki M, et al on behalf of the CF/Pancreas ESPGHAN Working Group and DIOS Study Group. International prospective study of distal intestinal obstruction syndrome in cystic fibrosis: Associated factors and outcome. *Journal of Cystic Fibrosis* 2016;**15**(4):531–9.

NICE 2015
National Institute for Healthcare and Excellence (NICE). Clinical knowledge summaries. Constipation in children (last revised June 2015). cks.nice.org.uk/constipation-in-children#!scenario (accessed 03 October 2016).

Penketh 1987
Penketh AR, Wise A, Mearns MB, Hodson ME, Batten JC. Cystic fibrosis in adolescents and adults. *Thorax* 1987;**42**(7):526–32.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rubinstein 1986
Rubinstein S, Moss R, Lewiston N. Constipation and meconium ileus equivalent in patients with cystic fibrosis. Pediatrics 1986; Vol. 78, issue 3:473–9.

Schunemann 2006
Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 13. Applicability, transferability and adaptation. *Health Research Policy & Systems* 2006;**4**:25.

Sterne 2011
Sterne JAC, Egger M, Moher D on behalf of the Cochrane Bias Methods Group, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor (s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from cochrane-handbook.org.

Tobias 2011
Tobias ES, Connor M, Ferguson-Smith M. *Essentials : Essential Medical Genetics*. 6th Edition. Hoboken, NJ, USA: Wiley-Blackwell, 2011.

Tuldahar 1999
Tuladhar R, Daftary A, Patole SK, Whitehall JS. Oral gastrografin in neonates: a note of caution.. *International Journal of Clinical Practice* 1999;**53**(7):565.

van der Doef 2010
van der Doef HPJ, Kokke FTM, Beek FJA, Woestenenk JW, Froeling SP, Houwen RHJ. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. *Journal of Cystic Fibrosis* 2010;**9**(1):59–63.

van der Doef 2011
van der Doef HP, Kokke FT, van der Ent CK, Houwen RH. Intestinal obstruction syndromes in cystic fibrosis: meconium ileus, distal intestinal obstruction syndrome, and constipation. *Current Gastroenterology Reports* 2011;**13**(3):265–70. [DOI: 10.1007/s11894-011-0185-9]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database/Resource	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	#1 Cystic Fibrosis *[MeSH descriptor]* #2 cystic fibrosis:ti,ab #3 fibrocystic near/10 disease near/10 pancreas #4 mucoviscidos*:ti,ab #5 cystic* near/10 fibros*:ti,ab #6 #1 or #2 or #3 or #4 or #5 #7 distal intestinal obstruction syndrome*:ti,ab #8 dios or mie:ti,ab #9 Intestinal Obstruction *[MeSH descriptor]*

(*Continued*)

	#10 meconium ileus equivalent:ti,ab #11 faecal near/3 (obstruction or impact*):ti,ab #12 Constipation *[MeSH descriptor]* #13 constipat*:ti,ab #14 laxative*:ti,ab #15 Laxatives *[MeSH descriptor]* #16 lactulose:ti,ab #17 Lactulose *[MeSH descriptor]* #18 (macrogol or polyethylene glycol*):ti,ab #19 Polyethylene Glycols *[MeSH descriptor]* #20 movicol:ti,ab #21 klean*:ti,ab #22 diatriozate:ti,ab #23 gastrografin:ti,ab #24 sennati:ti,ab #25 docusate:ti,ab #26 bicosulfate:ti,ab #27 acetylcysteine or fibrol:ti,ab #28 parvolex:ti,ab #29 fibre:ti,ab #30 picosulphate:ti,ab #31 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 #30 #32 #6 and #31
MEDLINE Ovid (1946 onwards)	1. Cystic Fibrosis/ 2. cystic fibrosis.tw. 3. (fibrocystic adj10 disease adj10 pancreas).tw. 4. mucoviscidos$.tw. 5. (cystic$ adj10 fibros$).tw. 6. 1 or 2 or 3 or 4 or 5 7. "distal intestinal obstruction syndrome*".tw. 8. (dios or mie).tw. 9. Intestinal Obstruction/ 10. meconium ileus equivalent.tw. 11. (faecal adj3 (obstruction or impact*)).tw. 12. Constipation/ 13. "constipat*".tw. 14. "laxative*".tw. 15. Laxatives/ 16. lactulose.tw. or Lactulose/ 17. (macrogol or polyethylene glycol*).tw. or Polyethylene Glycols/ 18. movicol.tw. 19. klean*.tw. 20. diatriozate.tw. 21. gastrografin.tw. 22. senna.tw. 23. docusate.tw.

(*Continued*)

	24. bicosulfate.tw. 25. acetylcysteine or fibrol.tw. 26. parvolex.tw. 27. fibre.tw. 28. picosulphate.tw. 29. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 30. 6 and 29
Embase Ovid (1974 onwards)	1. CYSTIC FIBROSIS/ 2. cystic fibrosis.tw. 3. (fibrocystic adj10 disease adj10 pancreas).tw. 4. mucoviscidos$.tw. 5. (cystic$ adj10 fibros$).tw. 6. 1 or 2 or 3 or 4 or 5 7. "distal intestinal obstruction syndrome*".tw. 8. (dios or mie).tw. 9. INTESTINE OBSTRUCTION/ 10. meconium ileus equivalent.tw. 11. (faecal adj3 (obstruction or impact*)).tw. 12. CONSTIPATION/ 13. "constipat*".tw. 14. "laxative*".tw. 15. LAXATIVE/ 16. lactulose.tw. or LACTULOSE/ 17. (macrogol or polyethylene glycol*).mp,hw. 18. movicol.tw. 19. klean*.tw. 20. diatriozate.tw. 21. gastrografin.tw. 22. senna.tw. 23. docusate.tw. 24. bicosulfate.tw. 25. acetylcysteine or fibrol.tw. 26. parvolex.tw. 27. fibre.tw. 28. picosulphate.tw. 29. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 30. 6 and 29
Clinicaltrials.gov	ADVANCED SEARCH **Search 1** *Search terms:* laxative OR laxatives OR lactulose OR macrogol OR polyethylene OR movicol OR klean OR diatriozate OR gastrografin OR senna OR docusate OR bicosulfate OR acetylcysteine OR fibrol OR parvolex OR picosulphate OR fibre *Study type:* Interventional Studies *Conditions:* cystic fibrosis **Search 2**

(*Continued*)

	Search terms: intestinal OR DIOS OR constipation OR constipated OR faecal OR meconium *Study type:* Interventional Studies *Conditions:* cystic fibrosis
ISRCTN Registry	ADVANCED SEARCH Condition: cystic fibrosis
WHO ICTRP	BASIC SEARCHES **Search 1**: cystic fibrosis AND intestinal **Search 2:** cystic fibrosis AND constipation **Search 3:** cystic fibrosis AND faecal **Search 4:** cystic fibrosis AND meconium **Search 5:** mucoviscidose ADVANCED SEARCH *Condition:* cystic fibrosis *Intervention:* laxative OR laxatives OR lactulose OR macrogol OR polyethylene OR movicol OR klean OR diatriozate OR gastrografin OR senna OR docusate OR bicosulfate OR acetylcysteine OR fibrol OR parvolex OR picosulphate OR fibre *Recruitment Status:* All
Open Grey	(cystic fibrosis OR cf OR mucoviscidos*) AND (intestin* OR constipat* OR faecal OR meconium OR laxative* OR lactulose OR macrogol OR polyethylene OR movicol OR klean* OR diatriozate OR gastrografin OR senna OR docusate OR bicosulfate OR acetylcysteine OR fibrol OR parvolex OR picosulphate OR fibre)

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	**Roles and respo**
TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage: draft the protocol	WC
Review stage: select which trials to include (2 + 1 arbiter)	JG + WC + FG as arbiter
Review stage: extract data from trials (2 people)	JG + WC
Review stage: enter data into RevMan	JG
Review stage: carry out the analysis	JG + WC

(*Continued*)

Review stage: interpret the analysis	JG + WC
Review stage: draft the final review	JG + WC
Update stage: update the review	WC

DECLARATIONS OF INTEREST

Jessica Green declares no known potential conflict of interest.

Dr Will Carroll declares no known potential conflict of interest.

Dr Francis J Gilchrist declares no known potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

Appendix 3: Summary of Findings table for the review: Interventions for Preventing Distal Intestinal Obstruction Syndrome in Cystic Fibrosis

Summary of findings:

Cisapride compared to placebo for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

Patient or population: preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis
Setting: Tertiary Centre
Intervention: Cisapride
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Cisapride				
Radiological diagnosis of DIOS (Diagnosis of DIOS) assessed with: Physician measured radiological scores follow up: range baseline to 6 months	No significant difference between cisapride and placebo.			34 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Radiologist scored for radiographic signs of DIOS
Adverse effects assessed with: Patient interviews follow up: range 3 months to 12 months	No adverse effects were noted.			34 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	
Total gastrointestinal symptom scores assessed with: Patient reported symptom scores Scale from: 20 to 100 follow up: range 3 months to 12 months	The mean total gastrointestinal symptom scores was **39.2**	The mean total gastrointestinal symptom scores in the intervention group was 7.6 lower (14.73 lower to 0.47 higher)	-	34 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	Made up of 10 different gastrointestinal symptoms: heartburn, flatulence, regurgitation, fullness, abdominal distension, abdominal pain, diarrhoea, nausea, vomiting, anorexia.

Summary of findings:

Cisapride compared to placebo for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

Patient or population: preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis
Setting: Tertiary Centre
Intervention: Cisapride
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Cisapride**				
Abdominal pain symptom scores assessed with: Patient reported symptom scores Scale from: 2 to 10 follow up: range 3 months to 12 months	The mean abdominal pain symptom scores was **5.9**	The mean abdominal pain symptom scores in the intervention group was 0.4 lower (2.05 lower to 1.25 higher)	-	34 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	
Abdominal distension symptom scores assessed with: Patient reported symptom scores Scale from: 2 to 10 follow up: range 3 months to 12 months	The mean abdominal distension symptom scores was **4.4**	The mean abdominal distension symptom scores in the intervention group was 0.9 lower (2.39 lower to 0.59 higher)	-	34 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	
Alterations in global symptom scores (Global symptom scores) assessed with: Patient reported symptoms scores follow up: range baseline to 6 months	With placebo: 3 felt better, 2 felt the same, 12 felt worse. With cisapride: 12 felt better, 2 felt the same, 3 felt worse. p<0.05			34 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,e]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

Summary of findings:

Cisapride compared to placebo for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

Patient or population: preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis
Setting: Tertiary Centre
Intervention: Cisapride
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Cisapride				

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Selective reporting may have occurred with this outcome. Allocation concealment and sequence generation was unclear
b. Cisapride is a prokinetic, not a typical laxative agent (Different to protocol). The study was conducted in 1990 when cisapride was still prescribed. It has now been taken out of the UK market and other international markets due to its rare but serious cardiac effects.
c. Very small number of participants in the study does not give sufficient information to give a precise effect estimate.
d. Allocation concealment and sequence generation ranked as unclear risk of bias
e. Allocation concealment and sequence generation ranked as unclear risk of bias. Physicians were also outcome assessors for this outcome, but there was no mention of blinding of the physicians.

Appendix 4: Survey questionnaire for the Management of Constipation and DIOS in Children with CF

Management of Constipation and DIOS in Children with CF

Q1 Are you:

- ❍ A consultant
- ❍ A doctor in training
- ❍ A doctor in a non-training post
- ❍ A specialist CF nurse

Q2 Siobhan is an 8-year old girl with CF. She is homozygous Phe508del and pancreatic insufficient. She has intermittently been constipated for 3 years. Mum tells you that she is passing small, hard, pellet-like stools (Bristol stool chart - type 1). Her diet is generally good and she is thriving. Her reported adherence to Creon is good. She is not currently taking any laxatives. A small faecal mass is palpable in the left iliac fossa. What is your first step in management? Select all that apply.

- ❑ Watchful waiting
- ❑ Lifestyle modification
- ❑ Start lactulose
- ❑ Start senna
- ❑ Start paediatric Movicol® (macrogol 3350 sachets)
- ❑ Start sodium docusate
- ❑ Start sodium picosulphate
- ❑ Start Gastrografin® (diatrizoate sodium solution)
- ❑ Start Klean-Prep® (macrogol 3350 formulated as bowel-prep)
- ❑ Start N-acetylcysteine
- ❑ Other (please specify) _____

Q3 What has helped you make these choices about a treating Siobhan's constipation? Select all that apply.

- ❑ Personal experience
- ❑ Local guideline
- ❑ Low quality evidence e.g. consensus, expert opinion, case reports
- ❑ High quality evidence e.g. randomised control trials, systematic review

Q4 Warren is a 10-year old boy with CF. He is homozygous Phe508del and pancreatic insufficient. He has intermittent lower abdominal pain. He reports opening his bowels twice per day, passing normal, formed stools without difficulty. His adherence with all treatments is good. On examination you identify a 6x4cm, indentable mass in the right iliac fossa. His abdomen is not distended and bowel sounds are normal. You make a diagnosis of incomplete DIOS. What is your first step in management? Select all that apply.

- ❑ Watchful waiting
- ❑ Lifestyle modification
- ❑ Start lactulose
- ❑ Start senna
- ❑ Start paediatric Movicol® (macrogol 3350)
- ❑ Start sodium docusate
- ❑ Start sodium picosulphate
- ❑ Start Gastrografin® (diatrizoate sodium solution)
- ❑ Start Klean-Prep® (macrogol 3350 formulated as bowel-prep)
- ❑ Start N-acetylcysteine
- ❑ Other (please specify) _____

Q5 Your treatment is unsuccessful. Warren is admitted to the paediatric ward with abdominal distension, pain and vomiting. The mass is still present in the right iliac fossa. An abdominal x-ray confirms bowel obstruction. You make a diagnosis of complete distal intestinal obstruction syndrome (DIOS). What is your next step in management? Select all that apply.

- ❑ Start lactulose
- ❑ Start senna
- ❑ Start Paediatric Movicol® (macrogol 3350)
- ❑ Start sodium docusate
- ❑ Start sodium picosulphate
- ❑ Start Gastrografin® (diatrizoate sodium solution)
- ❑ Start Klean-Prep®
- ❑ Start N-acetylcysteine
- ❑ Request a surgical review
- ❑ Other (please specify) _____

Q6 If Warren fails to improve with this treatment regimen, what would you do? Select all that apply.

- ❑ Continue the same dose of treatment(s)
- ❑ Increase dose of current treatment(s)
- ❑ Add in an additional treatment(s)
- ❑ Replace the existing treatment(s) with a different regimen

Q7 Which of the following clinical features would prompt you to ask for a surgical review? Select all that apply.

- ❑ Bilious vomiting
- ❑ Rebound tenderness and guarding
- ❑ Evidence of suspected perforation on repeat abdominal imaging
- ❑ Failure to improve with medical therapy after 24 hours
- ❑ Failure to improve with medical therapy after 48-72 hours
- ❑ Failure to improve with medical therapy after 96 hours
- ❑ Other (please specify) _____

Q8 What has helped you make the above choices about a child with CF and DIOS? Select all that apply.

- ❑ Personal experience
- ❑ Local guideline
- ❑ Low quality evidence e.g. consensus, expert opinion, case reports
- ❑ High quality evidence e.g. randomised control trials, systematic review

Appendix 5: Survey report for The Management of Constipation and Distal Intestinal Obstruction Syndrome at Cystic Fibrosis Centres in the UK.

The Management of Constipation and Distal Intestinal Obstruction Syndrome at Cystic Fibrosis Centres in the UK.

Green J[1], Carroll WD[1,2], Gilchrist FJ[1,2]

Running title: Management of constipation and DIOS in the UK.

Institutions: [1]Institute of Applied Clinical Science, Keele University, ST4 7QB, UK; [2]University Hospitals of North Staffordshire NHS Trust, Stoke on Trent, ST4 6QG, UK.

Correspondence: Dr Francis J Gilchrist, Department of Paediatric Respiratory Medicine, Royal Stoke University Hospital, University Hospitals of North Staffordshire NHS Trust, Stoke on Trent, ST4 6QG. Tel: 01782 675289. Fax: 0843 6365389. f.j.gilchrist@keele.ac.uk francis.gilchrist@uhnm.nhs.uk

Key Words: Constipation, cystic fibrosis, distal intestinal obstruction syndrome, laxatives.

Word count: 1097

Funding source: No funding was secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The other authors have no conflicts of interest to disclose.

Highlights:

- There is significant variation in treatment strategies for DIOS reported by cystic fibrosis clinicians.
- For incomplete DIOS, nine different interventions were combined into 22 different treatment regimens.
- The variation in the management of DIOS is likely to be a reflection on the paucity of good quality evidence.

- By comparison, there is far less variation in the management of constipation with Movicol® and lifestyle modification accounting for >70% proposed interventions.

Abstract

We surveyed consultants from paediatric and adult cystic fibrosis centres in the UK about constipation and distal intestinal obstruction syndrome (DIOS) management. Response rate was 55% (81/147). Movicol® and lifestyle modification accounted for >70% of the interventions used for constipation. Adult physicians used a higher median (range) number of interventions for constipation per patient; 2 (1-3) vs 1 (1-2), p=0.006. For incomplete DIOS, nine interventions, combined into 22 different regimens were used. The most common were Movicol®, Gastrografin® and lifestyle modification. Adult physicians were more likely to use Gastrografin® (p=0.01). For complete DIOS, Gastrografin®, KleanPrep® and surgical review were the most common interventions. Paediatricians were more likely to request surgical review (p=0.01). In summary, there was relatively little variation in the management of constipation. However, there was significant variation in the management of DIOS, particularly incomplete DIOS. This is likely to be influenced by the lack of good quality evidence.

Introduction:

Intestinal complications are common in children and adults with cystic fibrosis (CF).[1] Constipation affects up to half of all patients[2] and DIOS affects around 5% of patients in any one year[3]. Although these two conditions share symptomatology and treatments, the pathogenesis is different. DIOS is acute complete or incomplete faecal obstruction in the ileocaecum whereas constipation is gradual faecal impaction of the total colon.[4] Despite the high prevalence of constipation and DIOS in patients with CF there is no consensus regarding their treatment. We wanted to establish current UK practice at both adult and paediatric CF centres.

Materials and Methods:

Separate electronic surveys were devised to clarify the first and second-line treatments for constipation, partial DIOS and complete DIOS used by paediatricians and adult physicians. These were based around case vignettes of patients who met the diagnostic criteria for these conditions as defined by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition CF Working Group.[4] The surveys are available in Appendix 1. A link to the appropriate surveys was sent via email to each consultants listed on the UK CF Trust directory (2013). Consultants not listed on this directory were identified using each UK CF Centre's website. In total, links were sent to 82 Paediatricians and 65 Adult CF Physicians. If responses were not received within one week a single reminder email was sent out. The Chi-squared test was used to compare the response between paediatricians and adult physicians. A p value <0.05 was deemed

significant. All statistical analyses were undertaken using STATA version 12.0 (STATA Corp, Texas, USA). The UK NHS Health Research Authority ethics tool confirmed that ethical approval was not required (http://www.hra.nhs.uk/resources/before-you-apply/is-nhs-rec-review-required/).

Results:

Response Rate

We received responses from 51% (42/82) Paediatricians and 60% (39/65) Adult Physicians giving an overall response rate of 55% (81/147).

Summarising Free-Text Responses

Free text-responses related to fluid intake, exercise and adherence were grouped as "lifestyle modification" and those which included nil by mouth, IV fluids or nasogastric tube were grouped into "drip and suck".

Constipation

All respondents completed this question. The adult physicians used a higher median (range) number of interventions per patient than paediatricians; 2 (1-3) vs 1 (1-2), p=0.006. Responses are summarised in Figure 1. Sachets of Macrogol 3350 (Movicol®) and lifestyle modifications accounted for >70% of the responses from both paediatricians and adult physicians. Lactulose was the only other intervention used by paediatricians whereas the adult physicians also documented the use of sodium docusate, senna, N-

acetylcysteine and Gastrografin®. Adult physicians were more likely than paediatricians to recommend lifestyle modification (p=0.006).

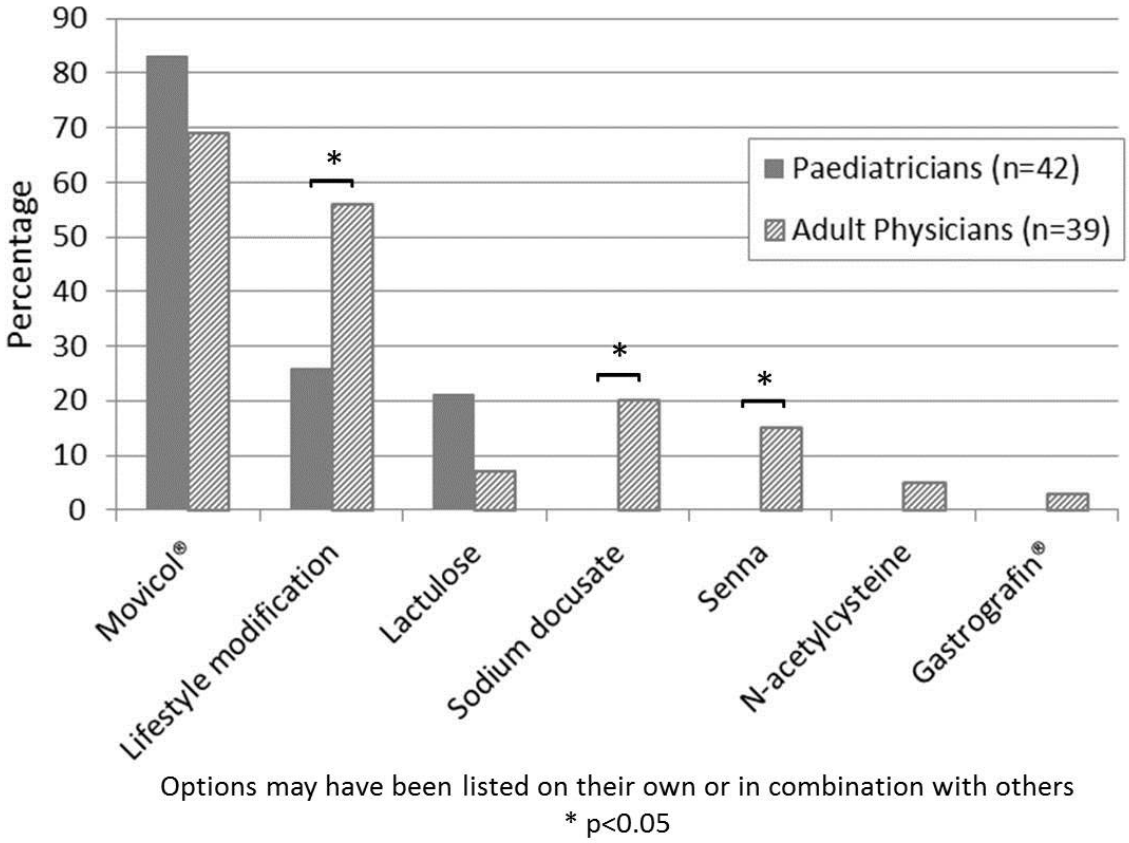


Figure 1: First line management for constipation.

Incomplete DIOS

Complete responses to this question were received from 39 paediatricians and 37 adult physicians. Responses are summarised in Figure 2. The nine options were combined into 22 different regimens by the paediatricians and 23 different regimens by the adult physicians. The three most commonly used interventions were Movicol®, Gastrografin® and lifestyle modification. Adult physicians were more likely to use Gastrografin®

(p=0.01) and there was a non-significant trend for paediatricians to use more lactulose (p=0.051).

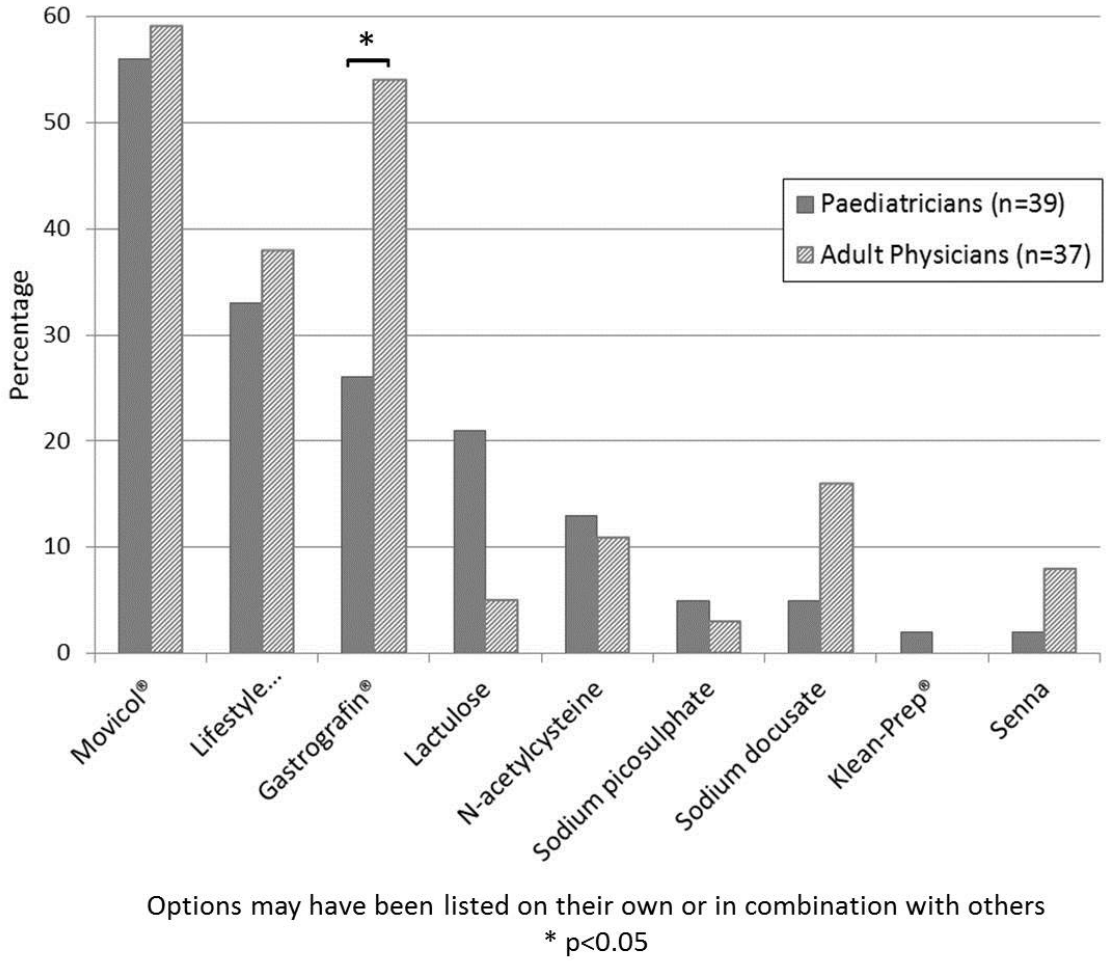
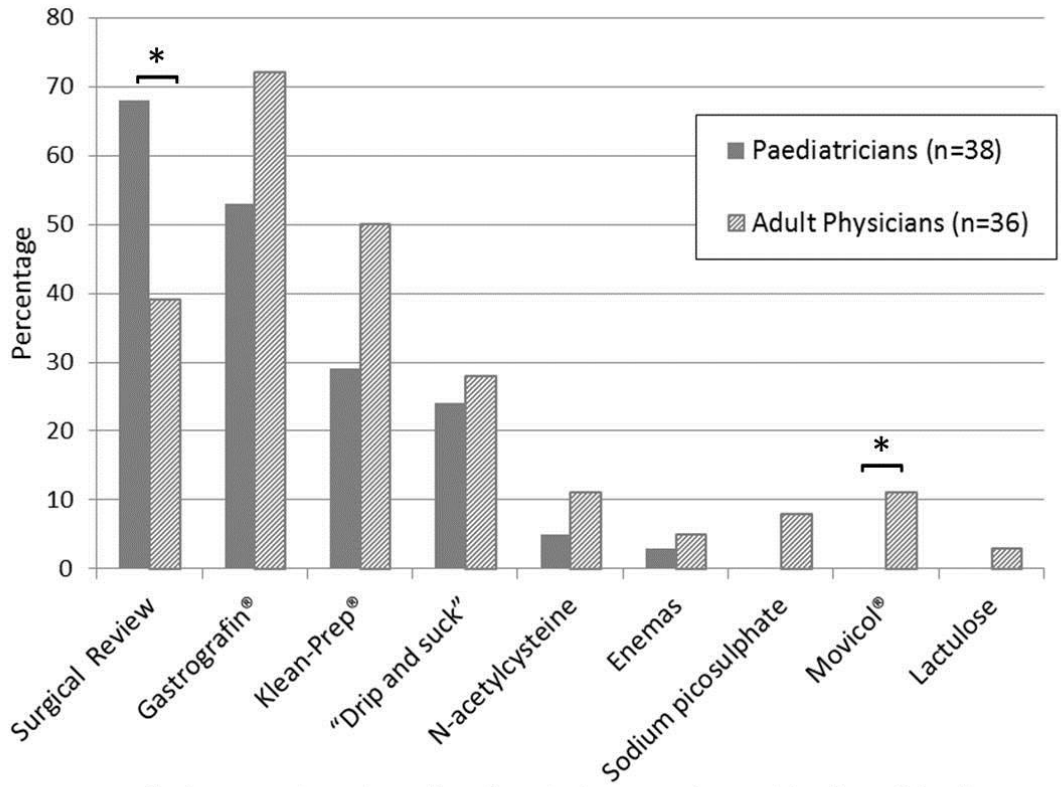


Figure 2: First line management for incomplete DIOS.

Complete DIOS

Complete responses to this question were received from 38 paediatricians and 36 adult physicians. Responses are summarised in Figure 3. The four most common interventions

were surgical review, Gastrografin®, KleanPrep® and "drip and suck". There was non-significant trend for adult physicians to use more Gastrografin® (p=0.08) and Klean-Prep® (p=0.06) than paediatricians. Paediatricians were more likely than their adult colleagues to ask for a surgical review as part of the initial management plan (p=0.01). When asked about signs and symptoms that would prompt asking for surgical review, paediatricians had a lower threshold with 36/38 referring if bilious vomiting was present compared to 12/36 adult physicians (p=0.0001).



Options may have been listed on their own or in combination with others.
"Drip and suck" includes mention of nil by mouth, intravenous fluids or nasogastric tube.
* p<0.05

Figure 3: First line management of complete DIOS.

Quality of Evidence

All of the adult physicians and all but one of the paediatricians identified a lack of good quality evidence on which to base their management decisions for patients with incomplete and complete DIOS.

Discussion

This survey has identified the first line treatment regimens for constipation and DIOS used for children and adults with CF across the UK. The surveys were distributed to the majority of paediatricians and adult physicians working at tertiary CF centres in the UK. The wide distribution and satisfactory response rate means that we are confident the survey accurately reflects current UK practice.

There was relatively little variation in the management of constipation in CF amongst both adult physicians and paediatricians. Although eight different therapies were listed the vast majority of respondents used macrogol 3350 and / or lifestyle modification as their first line treatment. Paediatricians only listed one additional treatment option. This consensus is likely to be influenced by the national guidance available for constipation, informed by randomised controlled trials.[5] Although the NICE guideline is not specific to cystic fibrosis, there is no reason to think that this guidance cannot be extrapolated to CF. Interestingly, adult physicians were more likely to recommend lifestyle changes than paediatricians. The reasons for this are unclear but may reflect adult patients being more willing or able to make such changes.

Although the respondents listed a large number of different regimens for the treatment of complete DIOS, Gastrografin® and Klean Prep® were the only commonly used medical therapies. This is in keeping with published guidelines.[6,7] Paediatricians were more

likely to request a surgical review than adult physicians. Surgical intervention is generally accepted as a last resort.[8] The different thresholds for surgical intervention may relate to the increased prevalence of DIOS in adults resulting in adult physicians being more used to seeing and managing such patients.

The widest variation in practice was seen in the management of incomplete DIOS with a large number of therapies being combined into multiple different regimens. This variation was noted amongst both the paediatricians and adult physicians. The listed medical therapies included both laxatives used for constipation and the bowel cleansing agents used to treat complete DIOS. Previously published guidelines have advocated the use of Movicol® as first line treatment for incomplete DIOS and gastrografin® as second line.[7]

This survey has highlighted wide variation in the treatment regimens used in DIOS for children and adults. This was most noticeable for incomplete DIOS. A lack of good quality evidence in this area is likely to be the underlying cause for this variation in practice. There is an urgent need for further research to clarify the optimal treatment of DIOS and develop patient reported outcome measures to assist in such studies.

Figure legends:

Figure 1: First line management for constipation.

Options may have been listed on their own or in combination with others. * $p<0.05$.

Figure 2: First line management for incomplete DIOS.

Options may have been listed on their own or in combination with others. * p<0.05

Figure 3: First line management of complete DIOS.

Options may have been listed on their own or in combination with others. “Drip and suck” includes mention of nil by mouth, intravenous fluids or nasogastric tube. * p<0.05

References

[1] van der Doef HPJ, Kokke FTM, van der Ent CK, Houwen RHJ. Intestinal Obstruction Syndromes in Cystic Fibrosis: Meconium Ileus, Distal Intestinal Obstruction Syndrome, and Constipation. Curr Gastroenterol Rep 2011;13:265–70. doi:10.1007/s11894-011-0185-9.

[2] van der Doef HPJ, Kokke FTM, Beek FJA, Woestenenk JW, Froeling SP, Houwen RHJ. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. J Cyst Fibros Off J Eur Cyst Fibros Soc 2010;9:59–63. doi:10.1016/j.jcf.2009.11.003.

[3] Cystic Fibrosis Foundation Patient Registry. Annual Data Report 2014. 2015.

[4] Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50:38–42. doi:10.1097/MPG.0b013e3181a6e01d.

[5] Constipation in children and young people: diagnosis and management | Guidance and guidelines | NICE n.d. https://www.nice.org.uk/guidance/cg99 (accessed May 9, 2017).

[6] Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros Off J Eur Cyst Fibros Soc 2011;10 Suppl 2:S24-28. doi:10.1016/S1569-1993(11)60005-2.

[7] Groves T, Kench A, Dutt S, Gaskin K, Fitzgerald DA. Question 8: How should distal intestinal obstruction syndrome [DIOS] be managed? Paediatr Respir Rev 2017;21:68–71. doi:10.1016/j.prrv.2016.04.001.

[8] Farrelly PJ, Charlesworth C, Lee S, Southern KW, Baillie CT. Gastrointestinal surgery in cystic fibrosis: a 20-year review. J Pediatr Surg 2014;49:280–3. doi:10.1016/j.jpedsurg.2013.11.038.

Appendix 6: Certificates of attendance from the Cochrane Review Author training courses.

Cochrane UK
Summertown Pavilion
18–24 Middle Way
Oxford OX2 7LG
UK
ukcc.cochrane.org

This certificate is awarded to

Jessica Green

Cystic Fibrosis & Genetic Disorders Group

For their attendance at
RA1 - Beginning a Systematic Review Protocol
18th October 2016

Martin J. Burt

Martin Burton
Director of Cochrane UK

Trusted evidence.
Informed decisions.
Better health.

Cochrane
UK

Cochrane UK
Summertown Pavilion
18–24 Middle Way
Oxford OX2 7LG
UK
ukcc.cochrane.org

This certificate is awarded to

Jessica Green

Cystic Fibrosis & Genetic Disorders Group

For their attendance at
RA2 – The Methods Section of the Protocol
19th October 2016

Mark J. Burt

Martin Burton
Director of Cochrane UK

Trusted evidence.
Informed decisions.
Better health.

Cochrane UK

Cochrane UK
Summertown Pavilion
18–24 Middle Way
Oxford OX2 7LG
UK
ukcc.cochrane.org

This certificate is awarded to

Jessica Green

Cystic Fibrosis & Genetic Disorders Group

For their attendance at
RA3 – Analysis Methods for Systematic Reviews
15th February 2017

Martin J. Burton

Martin Burton
Director of Cochrane UK

Trusted evidence.
Informed decisions.
Better health.

Cochrane UK
Summertown Pavilion
18-24 Middle Way
Oxford OX2 7LG
UK
ukcc.cochrane.org

This certificate is awarded to

Jessica Green

Cystic Fibrosis & Genetic Disorders Group

For their attendance at
RA4 – Advanced Topics in the Analysis & Reporting of Systematic Reviews
16th February 2017

Martin J. Burton

Martin Burton
Director of Cochrane UK

Trusted evidence.
Informed decisions.
Better health.