UNIVERSITY OF LIVERPOOL

Systematic evaluation of F508del variant specific therapies for people with cystic fibrosis

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

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Contents

Abstract

Background

Cystic fibrosis transmembrane conductance regulator (*CFTR)* modulating drugs called correctors aim to provide treatment for people with cystic fibrosis (CF) who have F508del variants in their *CFTR* gene. Novel correctors are currently being tested both in monotherapy, and in combination with other *CFTR* modulators, new trials need incorporating into systematic reviews and meta-analyses.

New therapies are tested in preschool children with CF (pscwCF); there is currently no agreed core outcome set for this group and it is unknown if measured outcomes are providing the most meaningful information for all stakeholders. We studied outcomes in this age group as the start of a process to develop a core outcome set (COS).

Methods

Cochrane review- An update of the Cochrane systematic review on correctors was performed. A comprehensive search of the Cochrane Cystic Fibrosis and Genetic Disorder Cystic Fibrosis Trials Register and eligibility assessment identified new parallel RCTs to include. Data on relevant outcomes was extracted and input into meta-analyses.

Review of outcomes- Cochrane systematic reviews including trials with pscwCF as participants were identified. From those reviews, we identified trials exclusively enrolling preschool children with CF. We found the protocols for each review and trial, where available. Outcomes stated in the protocol, methods and results for each review and trial were extracted and categorised into a group of themes reflecting treatment aspects of CF (airway, microbiology, extra-thoracic manifestation, patient/parent reported, nutrition, other- to include outcomes which don't fall under any of these themes).

Results

Cochrane review- 4 new trials were identified. 1 phase one examining a corrector in monotherapy and 1 phase one plus 2 phase two trials examining triple combination therapy (VX-659 or VX-445-tezacaftor-ivacaftor). At four weeks, pooled results for F508del/MF participants for triple combination regimens improved the CFQ-R respiratory domain versus placebo (MD 12.03 points (95% CI 8.36 to 15.71)). For relative change in FEV1, triple combination saw an improvement vs. placebo (MD: 22.78% [95% CI: 18.92, 26.63]. The mean difference for absolute change in FEV1 showed an improvement of 0.47 Litres [95%

CI: 0.40, 0.55] compared to placebo. Pooled absolute change in sweat chloride showed triple combination therapy led to a decrease compared to placebo (MD: -39.34 [95% CI: -43.04, -35.65]). Similar improvements were seen for participants with the F508del/F508del genotype. There was no statistically significant difference in adverse events and their severity between intervention and placebo groups in either genotype. There was no statistically significant difference in pulmonary exacerbation rates observed across the pooled results or between genotypes. All three of the triple combination studies were judged to have a moderate to high quality evidence.

Review of outcomes- We identified 29 eligible Cochrane systematic reviews which contained 295 trials, 10 of which were eligible for inclusion. For 6/10 trials, risk of bias was high (unclear in 3/10, low in 1/10). In the results sections of the trials, 65 different outcomes were reported 127 different times. The most common treatment related themes were other (outcomes which do not fit under other predefined themes, n=19) and airway (n=17). Least common treatment related theme was patient/parent reported (n=3).

Discussion

Cochrane review- There is insufficient evidence that monotherapy with correctors has clinically important effects in people with CF who have two copies of the F508del variant. Triple combination therapies (VX-445-tezacaftor-ivacaftor or VX-659-tezacaftor-ivacaftor), showed improvements in clinical outcomes for people with CF. At this stage, no significant safety concerns were identified, this will be further monitored with the emergence of longer-term data.

Review of outcomes- Despite a wide search, only ten eligible trials were found, six with a high risk of bias. A large number of different outcomes were measured, with the majority being surrogate biomarkers. There was a lack of pragmatic, longer term outcomes which give information about the lived experience of preschool children with CF and their families. Preschool years are vital for the future health of people with CF. A clear core outcome set would facilitate high quality research in preschool children with CF.

Acknowledgements

This year has flown by, and I would like to thank my supervisors, Professor Kevin Southern and Dr Ian Sinha for who have helped me with so much of their guidance, ideas and time. I would also like to thank them both for giving me countless opportunities to become involved in, which I would otherwise never have had the chance to experience. As a result of their support, I have grown in both ability and confidence in conducting and presenting research.

I would also like to thank Nikki Jahnke, Tracey Remmington and Dr Sarah Nevitt for their patience, time and invaluable advice when it came to conducting the Cochrane systematic review. An additional thank you to Professor Alan Smyth for his input into the core outcomes work.

To the University of Liverpool team at Alder Hey, thank you for welcoming me as part of the team for this year.

To my friends, family and loved ones; though only a couple of you actually had a clue what I've been up to all year, it didn't stop you giving all of your support as you have done all the way through university! Thank you.

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List of abbreviations

AE(s)	Adverse event(s)
BD	Twice daily
BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic fibrosis questionnaire-revised
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
COMET	Core outcome measures in effectiveness trials
COS	Core outcome set(s)
COS-STAR	Core outcome set-standard for reporting
COSMIN	Consensus-based standards for the selection of health measurement instruments
COST-CF	Core outcome set task force for cystic fibrosis
CYP3A4	Cytochrome P450 3A4
ENAC	Epithelial sodium channel
FEV_1	Forced expiratory volume after one second
FVC	Forced vital capacity
GP	General practitioner
GRADE	Grading of recommendations assessment, development and evaluation
ICER	Incremental cost-effectiveness ratio
JLA	James Lind Alliance
LCI	Lung clearance index
MD	Mean difference
MF	Minimal function
MHRA	Medicine & healthcare products regulatory agency
mg	Milligrams
mRNA	Messenger ribonucleic acid
NHS	National health service
NICE	National Institute for Health and Care Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs
OD	Once daily
OMERACT	Outcome measures in rheumatology
OR(s)	Odds ratio(s)
PSP(s)	Priority setting partnership(s)
pscwCF	Pre-school children with cystic fibrosis
RCT(s)	Randomised controlled trial(s)
WHO	World health organisation

Aims of this work

- Update Cochrane systematic review- Safety and efficacy of *CFTR* correctors for class II mutations (variants).
- Produce an up to date, systematic evaluation of outcomes reported in trials including pre-school children.

Variant nomenclature

The term “variant” is used throughout this dissertation as mutation is no longer considered an acceptable term. The first time a variant is described, it will be named using the Human Genome Variation Society (HGVS) nomenclature with the legacy name in brackets, for example c.1521_1523delCTT (F508del). Thereafter the legacy name will be used.

1. Introduction

Throughout medical school, I have found cystic fibrosis (CF) an interesting field concerning a variety of issues from the initial genetic defect to multi-system pathophysiology and novel high cost drugs. When I learnt about *CFTR* modulating drugs, I found them particularly fascinating. I had very basic experience of conducting a systematic review and wanted to build upon this to form important skills for an evidence-based practitioner and researcher of the future. I spent time with the CF team at Alder Hey and found there was an opportunity to combine these interests with the development of these skills and experience, as well as to contribute towards work that makes a difference to people with CF and their families. When undertaking this review, I found there a lack of guidance on the best, or most valuable outcomes for trials to measure in pre-school children with CF (pscwCF) and decided to pursue this further with the aim of laying the foundation for future work to improve the quality of research in pscwCF by developing a core outcome set for this population.

1.1 What is Cystic Fibrosis?

In people of Northern European descent, CF is the most common life-shortening genetic disease. 1 in 2000 Northern Europeans are born with cystic fibrosis (1). A genetic defect in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR)* gene leads to non-formation, or formation of a poorly or non-functioning *CFTR* transmembrane protein, which is typically found in cells at all epithelial surfaces throughout the body. This leads to abnormal salt transport (chloride, bicarbonate and anions) and deranged movement of water across membranes. In the lungs this leads to a decreased volume of airway surface liquid with impact on airway clearance through the mucociliary escalator. Decreased mucociliary clearance leads to a greater vulnerability to infections. Recurrent or chronic infection leads to chronic inflammation and progressive damage to the airways which eventually leads to respiratory failure. Abnormal ion transport in the pancreas leads to a fibrocystic pathology that impacts on exocrine and endocrine function with frequent malabsorption of products of digestion and sometimes diabetes mellitus. Excess loss of salt in sweat can lead to salt depletion. Other problems are described later.

CF affects approximately seventy thousand people around the world and is more common in people with ancestry from Northern Europe (2). In fact, a gradient of incidence is observed from the highest in the northwest to lowest in the southeast of Europe, reflecting a likely migration pattern of ancient civilisations from northern areas who spread across

Europe, carrying some of the first cystic fibrosis alleles with them. A recent paper suggests that it may have been those who spread their pottery skills across Europe (known as the Bell Beaker culture) who first carried CF across an entire continent (3). Currently, cystic fibrosis invariably leads to the shortening of a person's life. The Cystic Fibrosis Trust's (a UK charity dedicated to support those living with CF and their families, as well as promote research into its treatment) most recent annual data report found median survival of a person with CF in the UK to be forty seven years (4). According to the US National Institute of Health (NIH), Respiratory failure is the most common cause of death in people with CF (5). The Cystic Fibrosis Foundation (a US based non-profit organisation) registry in 2006 found 90% of reported deaths were cardiorespiratory failure (6), whereas the 2016 report found 67% to be due to the same cause (7).

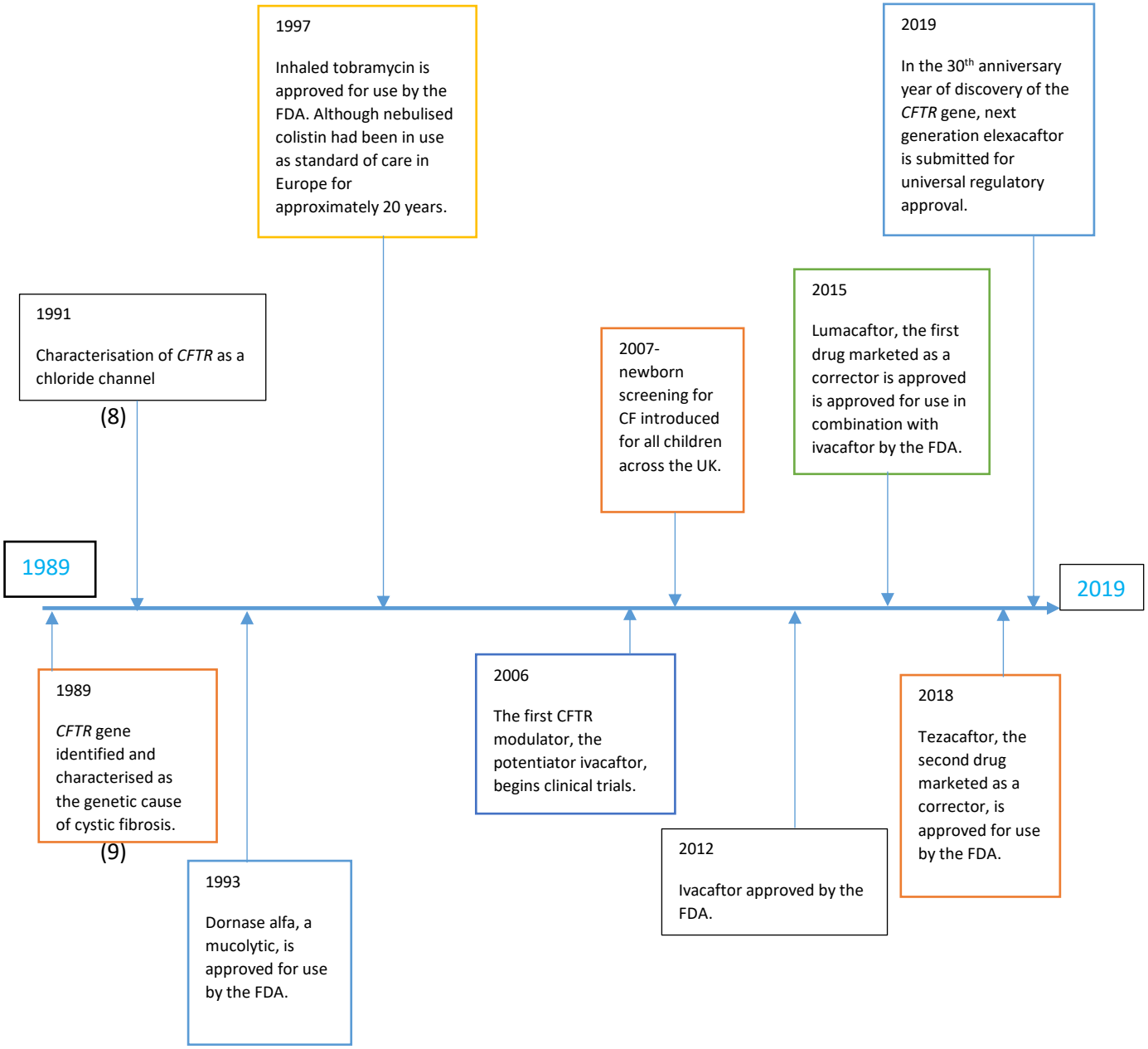

***Figure 1**: Timeline describing milestones in treatment of CF following discovery and characterisation of the CFTR gene as the cause of CF.*

1.2 Newborn screening

Newborn bloodspot screening for CF using the heel prick bloodspot card was introduced across the whole of the UK in 2007, but it had also been growing in availability around the country before this after the Cystic Fibrosis trust launched a campaign in 1996, when 80% of newborns were not screened for CF (10). In 2017, at the 10 year anniversary of the national screening programme, over six million newborns had been screened and almost 3,000 diagnoses of CF were made as a direct result of screening (10). Newborn screening leads to an earlier diagnosis than previous symptom-based diagnoses and therefore allows earlier intervention. There is also evidence that screening can lead to greater improvements in anthropometric measures of nutrition as an infant, through to benefitting survival rates as an adult with CF (11, 12).

1.3 Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) variants

The aetiology of CF stems from the inheritance of two CF causing variants in the *CFTR* gene, one from each parent. These variants lead to errors at different points along the processing pathway through which *CFTR* is synthesised. Over 1900 variants have been described and over 1500 of these are known to cause CF (13). The point on the *CFTR* processing pathway which a variant disrupts determines the classification of the variant.

1.3.1 Classification of *CFTR* variants

The different classes of *CFTR* variant are (13, 14):

- Class 1- No *CFTR* synthesis. Can occur due to frameshifts leading to premature stop codons and nonsense sequences, leading to degradation of mRNA before translation of the protein. Examples of this mutation include c.3846G>A (W1282X), c.1657C>T (R553X), and c.1624G>T (G542X).
- Class 2- Misfolded *CFTR*. Variants which can lead to an incorrectly folded *CFTR*, which is recognised as abnormal, retained in the endoplasmic reticulum and broken down before being transported to the cell surface membrane. Examples include c.1521_1523delCTT (F508del) (the most common mutation (13)) and c.3909C>G (N1303K).
- Class 3- Gating defect. Trafficking to the cell surface is successful in this class. *CFTR* channel is either closed or shows decreased opening. Can occur due to missense

mutations which disrupt how *CFTR* is affected by its usual regulatory factors. Examples: c.1652G>A (G551D), c.1651G>A (G551S).

- Class 4- Conductance defect. Trafficking to the cell surface is successful in this class. Missense mutations alter the shape of the channel, making it more difficult for chloride and bicarbonate ions to pass through. Examples: c.350G>A (R117H), c.1000C>T (R334W), c.1040G>C (R347P).
- Class 5- Decreased number of *CFTR* channels. variants leading to alternative splicing, disrupting mRNA which results in formation of both non-functional *CFTR* and a small number of functional channels at the surface membrane. Example: c.3140-26A>G (3272-26A-->G).
- Class 6- *CFTR* is functional but quickly removed from cell surface and broken down. Occurs as a result of variants that cause *CFTR* to be less stable when at the cell surface by increasing endocytosis of *CFTR* or decreasing its recycling back to the cell surface. Example: c.4197_4198delCT (4326delTC) (14).
- Some have suggested the formation of a seventh class of variant- "Unrescuable" variants, for example large deletions, which are unable to be rescued by current pharmacological strategies (14). Existence of this class has not yet been universally accepted.

It is useful to consider that classes 1, 2, 5, 6 (& 7) affect the quantity of functional *CFTR* at the cell surface membrane, whereas classes 3 & 4 affect the quality at which the *CFTR* functions when at the surface (see Figure 1 below) (15, 16). Variants are sometimes described as minimal function (class I & II), where little or no functional *CFTR* is synthesised, or residual function (class IV-VI), where a small amount of functional *CFTR* reaches the cell surface. Class III variants are referred to as gating variants due to their likely response to potentiators (16).

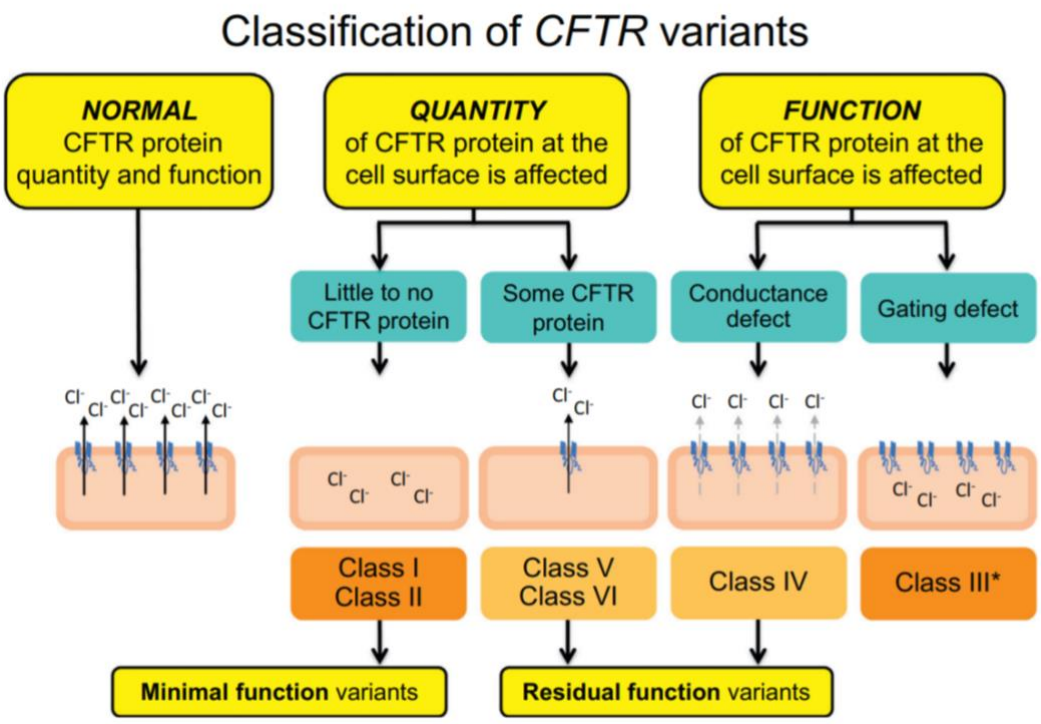

***Figure 2**: Relating the different types of variant to how it affects CFTR and what it means for its function. Used with permission from 'The increasing challenge of genetic counselling for cystic fibrosis' by Foil KE et al. Journal of Cystic Fibrosis, March 2019 (16).*

1.4 Treatment strategy

1.4.1 Relating treatment to pathophysiology

As mentioned above, due to *CFTR* being present on many epithelial surfaces around the body, the underlying defect in CF leads to numerous problems, making CF a multi-system disease. Notable manifestations of CF include the accumulation of, and difficulty in clearing highly viscous secretions in the airways, leading to increased vulnerability to respiratory tract infection, chronic inflammation leading to progressive airway damage and eventual respiratory failure.

CF can also lead to ineffective clearance of digestive enzymes from pancreatic ducts, leading to pancreatic damage and insufficiency. This inadequate release of digestive enzymes into the gastrointestinal tract causes decreased absorption of nutrients from the products of digestion meaning that people with CF can be malnourished and children may experience failure to thrive (17). It is considered a spectrum of severity, with the severity being influenced by the *CFTR* genotype combination which the person with CF possesses (18, 19). The CF Foundation's 2017 patient registry report states that as of its data

collection period, 85.7% of people on the registry were taking pancreatic enzyme replacement (7).

A further possible consequence of pancreatic damage and possible insufficiency is development of cystic fibrosis related diabetes mellitus (CFRD). The pathophysiology of this is multifactorial but a key component to note is the build-up of thick mucus in the pancreatic ducts causing obstructions which lead to inflammation and progressive damage to the pancreas, including its insulin-producing β cells- meaning the insulin producing capabilities of the pancreas are decreased; sometimes to the point where a person with CF is unable to adequately regulate their blood sugar levels (20-23). People with CF can also show decreased sensitivity to insulin due to the presence of infection and/or inflammation in the body plus the possible use of corticosteroids as part of their treatment (23). The 2017 UK CF registry report states that 29.8% of people aged over 10 years with CF in the UK were taking treatment for CFRD and an American study showed that the proportion of people with CF who were diagnosed with CFRD increased with age (24).

People with CF are at increased risk of developing low bone mineral density due to several risk factors including: reduced absorption of vitamin D and calcium, use of corticosteroids, potential for decreased physical exercise and possible hypogonadism (25, 26). Low bone mineral density becomes more common in people with CF as they get older, as well as with increasing severity of lung disease and malnutrition (26, 27).

It is a common occurrence in CF for bile ducts to become blocked, leading to inflammation, damage and eventually failure of the liver. Liver disease is the second most common cause of death in CF after lung disease, and accounts for 2-4% of deaths in those with CF (28-30).

The most common disease process occurring in the bowel of people with CF is obstruction (meconium ileus if present in a neonate, or distal intestinal obstruction syndrome). This occurs due to the disrupted regulation of salt & water in the lumen of the bowel leading to build up of extremely viscous meconium or stool.

1.4.2 Treating children with CF

Children with CF, especially pscwCF, are likely to have minimal lung disease in most cases and approaches to management are pro-active and preventative.

There are three principle treatment goals for children with CF:

- Maintenance of excellent nutrition
- Keeping the airway clear of infection
- Staying active & healthy

1.4.3 Universal/non-variant specific therapies

The treatments discussed in this section could be regarded as maintenance therapies to keep the person well, or reactive therapies to help the person get better or more stable following a deterioration of their health. They are independent of the different *CFTR* variants a person with CF may have, and are applicable to all people with CF.

Treatment also varies between the everyday maintenance therapies for a person with CF who is currently well, compared to when they develop acute problems. As the work discussed in this thesis focusses on regular treatments taken every day and not intended to address an acute problem, but more rather to prevent acute problems; we will briefly discuss the components of everyday CF management which are the cornerstones of keeping a person with CF as well as possible. Cystic fibrosis is an example of a condition where multidisciplinary input is of vital importance.

As we know, cystic fibrosis affects multiple different systems of the body in multiple different ways. It is important to address as many of these ways as possible in order to halt or slow progression of damage to the body's multiple affected systems. In children, this can be centred around the 3 main treatment goals above.

1.4.4 Excellent nutrition

CF specialist dietitians who support the optimum balance of nutrition and encourage intake of nutritious high energy foods as part of a healthy lifestyle (31). Cochrane systematic reviews of this area acknowledge the importance of optimal nutrition, yet also identify there is often a lack of high quality evidence for the optimum use of the interventions which they cover, which is not comprehensive (32-38).

1.4.4.1 Pancreatic enzyme replacement therapy & vitamin supplementation

Pancreatic enzyme insufficiency occurs when the exocrine pancreas is unable to produce and/or release adequate amounts of digestive enzymes into the digestive tract for digestion and absorption (17). Enzyme replacement aids with the breakdown & absorption of fats, proteins and carbohydrates. In addition, people with CF will also take supplements of the fat-soluble vitamins (A, D, E, and K) where required. Proton pump inhibitors or Histamine-2 receptor antagonists are often prescribed to make stomach chyme less acidic and aid the function of the enzymes. This also can improve the symptoms of gastro-oesophageal reflux that people with CF can experience (39, 40).

1.4.4.2 Hepatic disease

The mainstay of treating hepatobiliary complications in CF is to supplement bile acids in the form of ursodeoxycholic acid (41). Liver transplant is considered for profound portal hypertension or in rare cases, hepatic failure.

1.4.4.3 Intestinal disease

Meconium ileus or distal intestinal obstruction syndromes can occur due to stool that requires softening and removing by a combination of laxatives, intravenous fluids, N-acetylcysteine, pancreatic supplements and gastrograffin (39, 42). In severe cases, usually if the bowel is completely obstructed, surgery may be indicated. In some cases a colonoscopy may be an alternative to surgery (42).

1.4.4.4 CFRD

There is no clear consensus on the best approach to identify and manage CFRD. Typical treatment for CFRD is with insulin (23, 43).

1.4.4.5 CF related bone disease

Low bone mineral density- Options for treatment include vitamin D and calcium supplements and bisphosphonates. Some literature mentions the use of sex steroid replacement and supplement of anabolic agents such as parathyroid hormone or growth hormone, but less evidence is available for these and their use is less widespread (26). A Cochrane review examining bisphosphonates in CF shows them to be effective in increasing bone mineral density; their adverse effects are also important to be considered and monitored for (44). These range from nausea & vomiting, to oesophagitis, renal toxicity and jaw osteonecrosis.

1.4.4.6 Salt regulation

People with CF have impaired regulation of salt and water. This means they lose a higher amount of salt in their sweat. This salt needs replacing through supplementation (40).

1.4.5 Keeping airways clean

Respiratory disease is the most common cause of morbidity and mortality in CF (39). The main aims are to clear thick secretions from airways and promptly treat any respiratory infection (45).

1.4.5.1 Airway clearance:

The aim of this is to loosen secretions into the airway lumen to allow them to be coughed up. Before prescribing medications, it is important to involve CF specialist physiotherapists who can perform and teach manual airway clearance techniques, including postural drainage and the active cycle of breathing technique (46, 47). A Cochrane systematic review found that chest physiotherapy leads to clearance of more airway secretions compared to no chest physiotherapy (48). Physiotherapists can also encourage exercise which is vitally important for mucus clearance and aerobic health, and also provide expert input around devices which may prove useful, such as 'flutter valves' and oscillating vests (49). Short acting bronchodilators may also be given to aid the process of airway clearance (39). There are many Cochrane systematic reviews of physiotherapy interventions to aid airway clearance and aerobic health, with many highlighting its value. They also state that there is little evidence to show one technique to be superior in clearing airway secretions to others, and that airway clearance methods should account for what is most effective and fits with the preferences of the individual with CF. This is supported by the findings of a Cochrane meta-systematic review which combined the findings of other Cochrane systematic reviews (46, 50-53). Although one review did find positive airway pressure physiotherapy to lead to a lower rate of pulmonary exacerbations (54).

1.4.5.2 Antimicrobial prevention & therapy:

Prevention of infection is important and the Cystic Fibrosis Foundation (CFF) recommend guidelines for infection prevention and control, they include: clinicians using contact precautions e.g. gloves & aprons, separating people with CF by at least 6 feet to avoid droplet transmission, hand washing for the person with CF and their close contacts and clinicians. The guidelines also recommend people with CF can wear surgical face masks when in a healthcare environment (55). As well as such precautions, people with CF should receive all routine vaccinations, including influenza and pneumococcal vaccines (56, 57).

Currently, guidelines state there is insufficient and conflicting evidence to support the use of palivizumab to prevent infection with respiratory syncytial virus in young children with CF (57-61). Further important methods of prevention are to perform routine respiratory cultures and for clinicians to have a low threshold to perform bronchoscopy & take samples.

Pseudomonas aeruginosa is an important pathogen in CF as it is linked with a more rapid deterioration in the lung function of people with CF. It is typically not recommended to take continuous prophylactic antibiotics against pseudomonas as multiple trials have shown there to be no overall benefit to people with CF (45, 62-64). NICE (National institute for health & care excellence), the UK body who use evidence-based approaches to determine best practice guidelines and advise the UK government on commissioning therapies, also does not recommend prophylactic antibiotics against other clinically significant pathogens in adults with CF who are currently well. NICE do however recommend prophylaxis against respiratory *Staphylococcus aureus* in children up to the age of three years, and consider continuing its use up to six years of age (31). Antibiotics can be very useful in efforts to eradicate bacterial infections and to prevent them becoming a chronic infection, with early identification and treatment being paramount, hence the importance of routine cultures and low threshold for bronchoscopy (39, 65). As a result of its negative effects on pulmonary function *Pseudomonas* is an example of a pathogen which should be targeted for eradication. There is however uncertainty as to the best approaches toward eradication therapy; the TORPEDO-CF study (awaiting publication at time of writing) found there to be no significant difference between intravenous ceftazidime and tobramycin combination antibiotic therapy versus oral ciprofloxacin in the eradication of early infection of *Pseudomonas aeruginosa* in people with cystic fibrosis (66).

1.4.5.3 Mucolytic therapy:

This aims to assist with airway clearance by making the secretions less viscous. There are multiple inhaled agents including an enzyme which breaks down DNA in inflammatory cells in the airway (Dornase alfa). A Cochrane review found that dornase alfa can be taken at a time near to airway clearance techniques that is preferred by the individual (67). Osmotic agents draw water into the secretions (mannitol). A Cochrane review examining inhaled mannitol in people with CF found it to improve pulmonary function, but not quality of life versus control (although this was based on low quality evidence) (68). Finally some agents work by multiple mechanisms of action such as osmotic action, disrupting ionic bonds and dissociating DNA in the secretions to facilitate proteolysis (hypertonic saline) (39, 69). A

Cochrane review found nebulised hypertonic saline to lead to improvements in pulmonary function, and an RCT found it to lead to statistically significantly lower occurrence of pulmonary exacerbations versus control (see figure 3 below) (67, 70). Another Cochrane review recommends inhaling hypertonic saline twice a day and states that despite there not being a difference in measured pulmonary function, taking it before or during airway clearance techniques leads to a greater feeling of satisfaction compared to inhaling it after these techniques (71). A recent multicentre randomised placebo-controlled trial (Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP)) found hypertonic saline to be safe and to lead to a statistically significant decrease in $LCI_{2.5}$ (the number of times an individual's total lung volume will pass through their lungs for the concentration of a tracer gas to reach 2.5% of its concentration at the start of the test) versus isotonic saline placebo (mean treatment effect -0.63 $LCI_{2.5}$ units, 95% CI -1.10 to -0.15, p=0.010) in children aged 3-6 years (72). This suggests that inhaled hypertonic saline could be offered routinely to young children as part of their treatment, but an important consideration made in a comment on this trial states that the extra treatment burden of this extra intervention should also be considered (73).

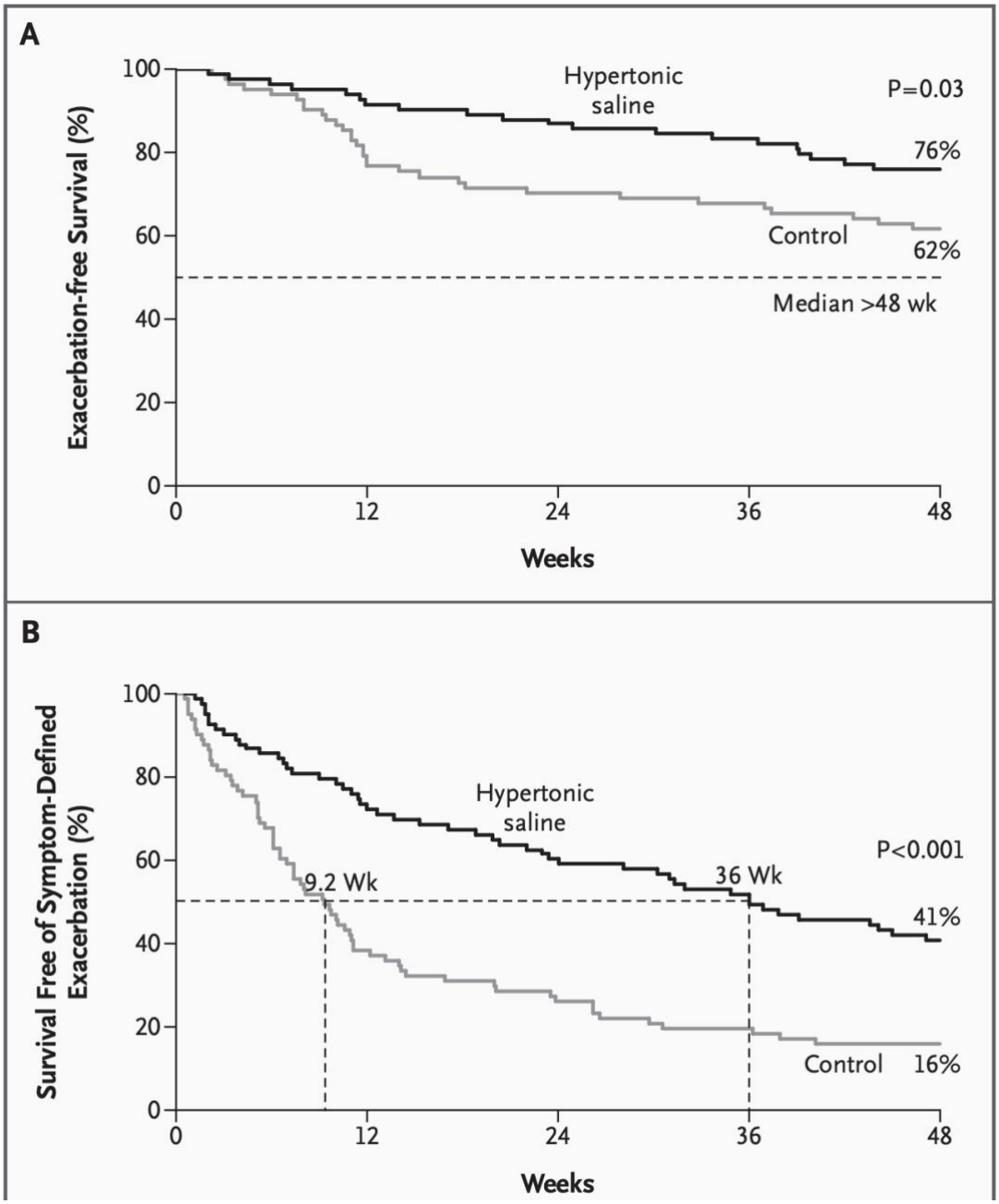

***Figure 3**: Kaplan-Meier survival plots showing inhaled hypertonic saline leads to significantly less pulmonary exacerbations at given time points. From Elkins et al. NEJM 2006 (70).*

Kaplan-Meier survival plots show the number and rate of occurrence of events, in this case pulmonary exacerbation. Each time a person suffers a pulmonary exacerbation. The line for their group (intervention or placebo) moves down. In Figure 3 we can see that hypertonic saline led to a less people having a pulmonary exacerbation versus placebo at any given time point (70).

1.4.5.4 Airway inflammation:

Inflammatory processes in CF airways are dominated by neutrophils. This chronic state of inflammation has been shown to be damaging to the airways (74). There are multiple pharmacological approaches to reduce inflammation in the airways. Notably anti-inflammatory agents such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective at reducing inflammation, however it is important to consider their known adverse events (39, 65, 75-79). A Cochrane systematic review found long term oral corticosteroids to slow progression of lung disease, but noted the significance of adverse events, suggesting a risk-balance analysis of alternate day low-dose regimens may be useful (80). The Cochrane review examining NSAIDs in cystic fibrosis has shown high-dose ibuprofen to slow progression of lung disease (75).

1.4.6 Staying active & healthy

It is important for people with CF to exercise for numerous reasons. Exercise helps maintain lung function and improve airway clearance (81). Through improved exercise tolerance it can help against shortness of breath (82). Exercise can also potentially help manage CFRD through improving sensitivity to insulin and decreasing systemic inflammation (83). Additionally exercise can also maintain bone mineral density (84), as well as potentially help decrease levels of anxiety & depression (85). Another benefit of using exercise as an intervention is that it typically has very little, if any adverse events. A Cochrane review examining this intervention says that further work would be useful to determine the optimum balance of a combination of aerobic and anaerobic exercise in CF (86).

1.4.7 CF and fertility

Women with cystic fibrosis are able to become pregnant but may find it more difficult to conceive due to a poorer nutritional status and/or thicker cervical mucus (87). Around 98% of males with CF have congenital bilateral absence of the vas deferens but cystic fibrosis would not typically cause a problem with the sperm itself, meaning sperm can still be extracted and used to conceive by means such as in vitro fertilisation (88).

1.5 Therapies which address the underlying defect

The components mentioned above have formed the main pillars of CF treatment for a long time and contribute to a significant treatment burden. In the past 10 years, a new approach has emerged: using small molecule drugs which directly target the underlying defect in the *CFTR*.

1.5.1 Potentiators

An example of a potentiator is ivacaftor, a medication taken orally twice a day. Potentiators help improve the function of the *CFTR* protein at the cell membrane by increasing the probability that a *CFTR* channel will be open at a given point in time, meaning it can be used independently (as monotherapy) in people with CF who have class III or IV variants in their *CFTR*, which has already made it to the cell surface (89). This intervention has remarkable impact for people with CF who have the G551D and other class III *CFTR* variants (90, 91). The findings were so profound that the effects of ivacaftor for those with applicable class III and IV variants are now considered the benchmark against which other variant specific therapies should be compared.

1.5.2 Correctors

Though effective for the above classes of variants, there is no evidence to suggest ivacaftor alone provides benefit to those with the F508del variant (91). This is to be expected, as ivacaftor requires *CFTR* to be present at the cell surface membrane in order to potentiate its opening. This means that ivacaftor alone is not a suitable therapy for the large proportion of people with CF who don't have a class III or IV variant.

In class II variants where there is a problem with folding of the *CFTR* before it reaches the cell surface, the folding must first be corrected to reach the cell surface. Before F508del variant specific drugs were synthesised, it was demonstrated in 1997 that the folding & trafficking defect of the class II F508del variant can be corrected by lowering the temperature of the cell. It was shown that by incubating *CFTR* proteins with the F508del trafficking defect at 26 degrees Celsius for 2 days led to formation of folded, functional *CFTR* channels (92). This served to show that it was possible to overcome the defects in folding and trafficking to the surface and formed the basis of work into possible therapies to help correct the F508del variant of the *CFTR* protein.

Medications such as lumacaftor and tezacaftor are known as correctors. Correctors aim to address class II variants, including F508del. Approximately 80-90% of people with CF have at least one copy of a class II variant with 70% of people with CF from European descent specifically having F508del (13). Correctors aim to mask the abnormal folding of the *CFTR* protein, which is defective in the presence of F508del (89). This allows the *CFTR* to reach the cell surface membrane, restoring the transport of salts (93-95). The ion transport properties of this corrected channel may be augmented further by adding the potentiator, ivacaftor as a co-formulation with a corrector to increase function of the *CFTR* once it has reached the cell surface.

1.5.3 Ataluren & other "skipping" modulators

Class I variants occur due to the abnormal presence of premature termination codons. This class of therapy, an example of which is ataluren, aim to mask the presence of these codons and enable read through of the *CFTR* gene to create a functional ion channel protein. The most recent Cochrane review on ataluren for CF states that there is currently insufficient evidence for the use of ataluren in CF, that it is associated with potentially significant adverse events such as renal impairment and more research into compounds to treat this class of mutation would be valuable (96).

1.5.4 Amplifiers

Currently in development and testing are other classes of *CFTR* modulating drugs such as amplifiers, which act to increase the amount of *CFTR* protein synthesised by a cell. They could prove useful in combination with potentiators and correctors, as well as allow more classes of variants to be treated with *CFTR modulation*, such as class V and VI variants. An example of an amplifier is PTI-428, a drug which has been tested in monotherapy and in combination with a potentiator and corrector, with results looking promising (97, 98).

1.6 Safety, cost and the need for evidence.

All new therapies need robust safety monitoring. This can be challenging due to the fact that studies are not powered to detect adverse events as in order to detect uncommon/rare but serious adverse events, the study may have to enrol thousands of participants, which is typically not feasible. There is also the possibility of 'unknown unknowns' meaning that therapies may lead to side effects we have never considered and therefore it is hard to know what safety measures are most appropriate or what adverse events may occur due to a particular therapy. A system used in the UK is the yellow card scheme from the MHRA, an example of which can be found in the appendix. A recent Cochrane review found both lumacaftor/ivacaftor and tezacaftor/ivacaftor to have modest improvements versus placebo in multiple outcomes including pulmonary function, quality of life and rates of pulmonary exacerbation. It also found tezacaftor/ivacaftor to have a better safety profile, as it did not show the adverse effects associated with lumacaftor/ivacaftor which included transient increases in shortness of breath in the short term, and increases in blood pressure in the longer term (99). Unlike lumacaftor, tezacaftor is not an inducer of CYP3A4 enzymes and does not exhibit as many drug-drug interactions as lumacaftor, which also affects the metabolism of its co-administered ivacaftor (tezacaftor does not affect ivacaftor metabolism) (100).

These new medications are under a period of exclusivity for the pharmaceutical company that developed them, this accounts for their high cost. The British National Formulary reports a 28 day supply of ivacaftor to cost £14,000 (101). That equates to £250 per tablet or £500 per day. High costs have impacted the availability of these types of drugs in many countries, including the UK. NICE has performed a health technology assessment and formulate an incremental cost-effectiveness ratio (ICER) for lumacaftor/ivacaftor to assess if it is cost effective for the NHS to invest in this medicine. It was conducted in those aged over 12 years with homozygous F508del, and resulted in NICE not recommending this formulation (102). In those aged 12 years or under however, this medication is sometimes prescribed. This can lead to considering managed access schemes, where these medicines can be accessed on a compassionate basis. It should be noted that the issue of accessing high cost medications is not exclusive to CF and the ultimate decision as to whether to fund medicines in the UK lies with the government, taking the information provided by NICE into account.

One way of collecting useful information to help make these decisions about whether such medicines are safe, effective and cost-effective to start or continue is by conducting a

systematic review. This applies for all new therapies whose efficacy and safety data should be collated in order to synthesise one of the highest levels of evidence to help decide whether interventions are safe and effective.

2. An introduction to systematic review.

2.1 Cochrane Collaboration

An epidemiologist named Archibald Cochrane worked as the sole medical officer for 20,000 German prisoners of war during the Second World War. Despite many falling ill and Dr Cochrane being unable to treat them all, only one of these men died due to illness. This made Archie consider that many illness processes are self-limiting and if the treatment he was giving was making any difference. He proposed the foundations of systematic review, and in doing so, prevented people experiencing unnecessary side effects and inefficacious treatments (103).

He became an advocate of the importance of randomised controlled trials and called for a database to which they all should register. He also stressed the value of appraising the quality of research. It was only after he passed away in 1988 that the Cochrane Collaboration was formed (104). The collaboration brings together a network of various people who can play an important role in creating accessible and credible resources to inform health decisions (105). The register Archie Cochrane campaigned for now has over 400,000 entries and is used to create high quality systematic reviews (103).

The collaboration has created a process and structure to adhere to in order to create a systematic review of the highest standard. They produce a handbook to lay out the requirements and processes which must be fulfilled (106). Particular focus is made on assessing the credibility of the evidence, particularly the risk of bias (107). Combined with a rigorous and open peer review and editorial process, this means that Cochrane reviews are considered one of the most credible tools to aid decision making.

2.2 What is a systematic review?

A systematic review is a way of collecting all the available (and relevant) information to answer a pre-defined research question. It should follow systematic methods with the aim to reduce bias to draw more reliable conclusions (108, 109).

According to the Cochrane Handbook for Systematic Reviews of Interventions (106), a systematic review has multiple key, defining features: a methodology which has been

decided *'a priori'* and recorded in an explicit manner so that others can replicate it. This methodology includes clear objectives and criteria for which studies are eligible for inclusion in the review. The search methods ensure that all studies and sources of information which fulfil these criteria are identified, their quality can be assessed (typically using risk of bias as a measure) and their data extracted, synthesised and presented in an ordered fashion.

If there is a sufficient amount of data, systematic reviews incorporate a meta-analysis into their data analysis. Meta-analyses employ statistical methods in order to combine results of trials and determine if there is an overall benefit towards the new intervention, against the placebo or current standard of care. It can also illustrate if any difference is significant or not- are the results due to chance or does the intervention make a meaningful difference?

Meta-analyses are often represented as a forest plot. This gives us a visual representation of different trial outcomes and the pooled data.

Its horizontal axis shows us the statistic which is being examined. It can show a relative statistic such as odds ratio or risk ratio, or it can show an absolute statistic such as absolute risk or standardised mean difference. The vertical axis in the middle of the plot, or the line of null effect intersects the horizontal axis at either 1.0 or 0 for relative and absolute values, respectively. This indicates the point where the exposure has no effect on the outcome, or there is no difference between interventions. The diamond indicates the overall result, with its width showing the spread of the results by showing 95% confidence intervals. Typically, larger sample sizes lead to narrower confidence intervals, as we are more confident about where the where the true result lies.

If the outcome which your statistical figure measures is desirable e.g. remission, then results on the right of the plot show that the intervention has had a positive effect compared to the control group- the intervention is more likely to lead to the positive effect than your control group.

If the outcome you are examining is undesirable, e.g. death, then it is the results on the left of the plot which favours your intervention- the intervention decreases the probability of the negative event occurring compared to control.

Each study is represented by a square. The study's confidence intervals are shown by a line spanning through the square. The wider the line, the bigger the confidence intervals and the less reliable are the study's findings.

There is a diamond on the forest plot which represents the overall treatment effect of our intervention- whether the total finding of the meta-analysis favours the intervention, following the same logic as above. If the diamond crosses over the line of null effect however, this indicates the result is not statistically significant and that there is no real difference between intervention and control.

Forest plots can also give a visualisation of homo/heterogeneity. If all squares/diamonds are favouring the same direction of effect with similar magnitudes, the results are homogeneous: there is less variation between the results, and they are more likely to be indicating a true effect.

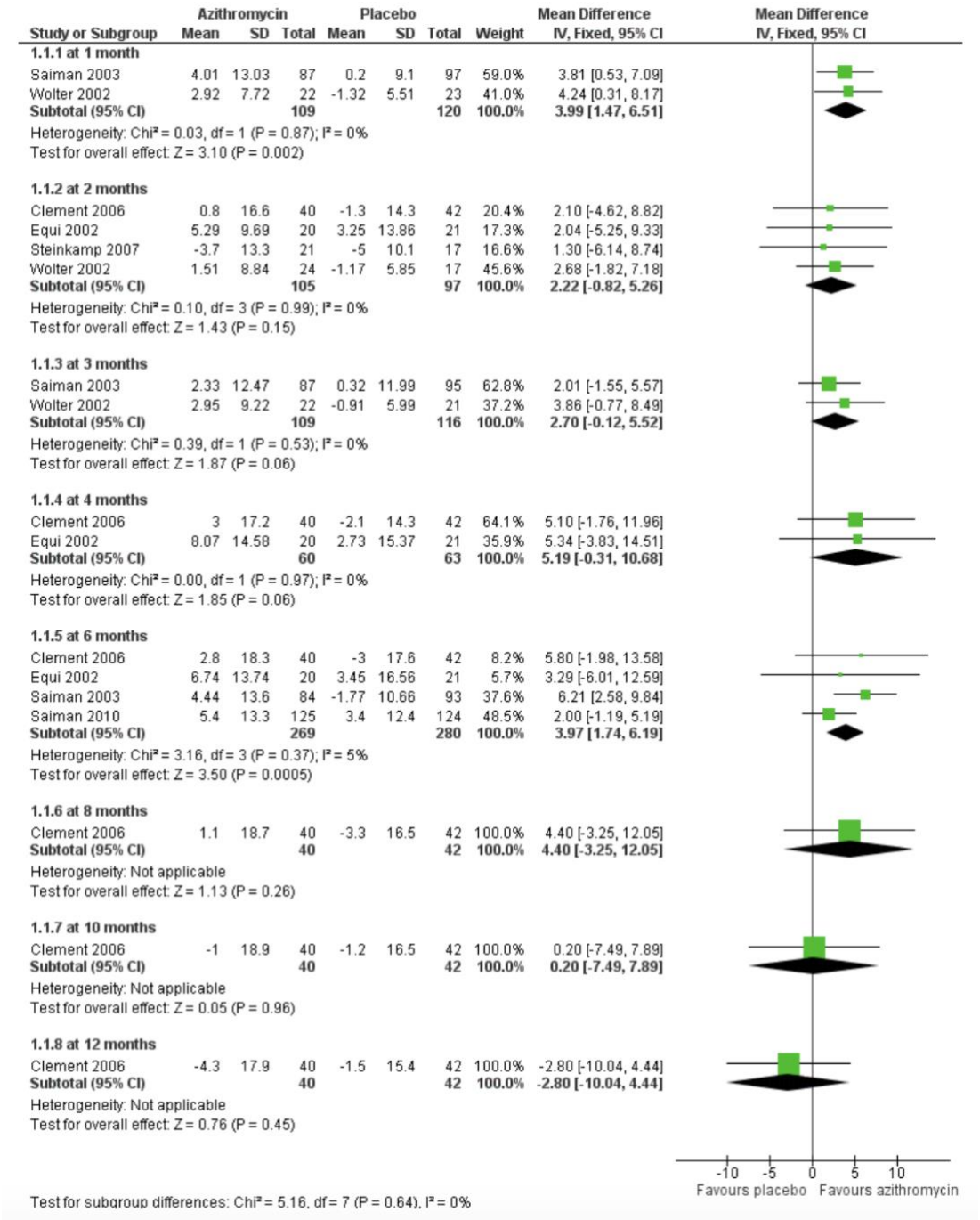

***Figure 4**: Example of a forest plot for Cochrane systematic review of azithromycin in CF. From Southern KW et al. Jan 2012 (110)*

The above forest plot shows a meta-analysis for the effect of azithromycin on relative change of percent predicted FEV_1. This shows grouped data at different time points showing consistency until later time points, where development of heterogeneity should be noted. Individual trials are each represented by a square. The size of the square represents its weight, which is influenced significantly by the number of participants in the study. The line going through each square is the 95% confidence intervals for that study's result. The

diamond represents the meta-analysis at each time point. The smaller the diamond, the greater the confidence around the result.

2.3 Why do a systematic review?

The quantity of evidence, and its likely range of quality, creates a challenge for stakeholders to find the best source of valid information to answer their questions. The sourcing of such information is time consuming.

A systematic review can form part of the solution to this, where a smaller number of people with the means to synthesise such evidence, find all the applicable information and can evaluate the quality of this information in order to provide a (relatively) accessible and succinct summary for decision makers to access.

Systematic reviews are considered one of the highest levels of evidence based methodology (111). With rigorous standards, they combine the highest quality of primary research (Randomised controlled trials (RCTs)) to ascertain a more reliable answer to a research question. They employ statistical techniques such as weighting to further increase the reliability of their meta-analysis and comment on the quality of evidence which they synthesise. Should the authors choose (and therefore state in their protocol), systematic reviews can also incorporate data from sources and trials other than RCTs. This can have varying effects on the quality of included data (as can variation in quality of RCTs).

2.4 The challenge of systematic reviews

The rigid nature of systematic reviews rules out many of the “what ifs” you may see in clinical practice. Moreover, different decision-making groups may have different questions. A GP in London named Trisha Greenhalgh wrote a piece titled ‘Why are Cochrane reviews so boring?’ (112). Within this she comments that by the process of extracting the raw data to answer a “tightly focused question”, we may lose the ability to use the review for the actual questions we ask, or will be asked in practice. In addition, she suggests another “Cochrane Database of Editorials, Ideas and Opinion Pieces”, perhaps with the idea of complementing the facts & figures of a Cochrane review with real world experience. However, this may also run the risk of conflating facts and opinions at the stage of providing evidence, before discussions are held at local, regional, national etc. level to decide guidelines or commission services.

2.5 Heterogeneity

Systematic reviews can include many studies. Though these studies should examine the same or as similar as possible interventions, populations, etc. there may be some differences between the results and conclusions which they report. If these differences are down to chance, that can be assessed but can still have an effect on the strength of recommendations. There may be some differences, or heterogeneity between their methodologies (methodological heterogeneity), the characteristics of the studied participants (clinical heterogeneity) or the way in which results are measured or reported (statistical heterogeneity) (113, 114). It is possible to identify and measure the amount of heterogeneity using a funnel plot and the I^2 statistic (115). This allows us to quantify heterogeneity, acknowledge it and consider the effect on conclusions. This is a strength of systematic review in that it identifies such limitations in an evidence base and the need for a greater amount of high-quality research in a given field.

3. Core outcome sets for cystic fibrosis

As I undertook the systematic review of correctors for CF, I started appreciating the importance of valid clinical outcome measures and the lack of a core outcome set for people with CF. This problem was particularly apparent in pscwCF, for whom little work on core outcomes has been performed. In this section I describe the importance of core outcome sets and later I report a study of outcomes reported in trials of pscwCF.

3.1 What is a core outcome set?

A core outcome set (COS) is an agreed & standardised set of outcomes which lays out the minimum requirements on which outcomes should be measured for trials looking at a similar combination of condition, intervention and patient group or in a specific field of interest (116-118). Formed by consensus and input of multiple stakeholder groups, the aim is that all trials examining similar conditions, participants and interventions will adhere to these standards (118). This will lead to an improvement in the consistency of results between trials, leading to a decrease in the use of subgroup analyses which can produce lower quality results. This ensures the data produced from research has a higher level of validity. In order to encourage uptake of the core outcome sets, it is important that the sets are created with a rigorous methodology. The core outcome set- standards for reporting (COS-STAR) framework highlights the value of this as well as the importance that the processes of creating a core outcome set are recorded and accessible for researchers in order to ensure transparency throughout the research process (118).

3.2 The importance & value of core outcomes

A possible limitation that can be identified by a systematic review is that trials can test the same/similar interventions in the same/similar population but measure different outcomes. This variability can make the process of collating evidence for systematic reviews more difficult. In 2010, the most frequently accessed and cited Cochrane systematic reviews described difficulties created by variations in outcome reporting (119). By creating a COS, more data can be directly used in a systematic review and therefore conclusions can be drawn with greater confidence that the evidence will translate to practice, with outcomes that are more meaningful to stakeholders. This reasoning can be applied to all populations, interventions and specialities where research trials are conducted.

Trials concerning variant specific therapies have largely been tested in adults, adolescents and older children. Though some trials have now began including 0-5 year olds, for

example, the KIWI trial, which examined Ivacaftor in 2-5 year olds with at least one class 3 (gating) variant (120), less is still known if these drugs are safe and effective (or not) in pre-school children. Trials in pscwCF have tended to be open label, with the assumption that efficacy data are translatable from trials on older patients. This is understandable and part of most paediatric investigation plans, but there should be an effort to determine effectiveness in this age group, despite the challenges.

Efficacy outcomes can be measured well in RCTs, as changes are often detected within the trial period. However, they are not always translatable to patients outside of the clinical trial. Outcomes may indicate efficacy within the trial but not indicate how this efficacy will impact the everyday wellbeing of patients.

Core outcome sets can also help overcome selective outcome reporting by stating the expectations of what should be reported and raising awareness among authors and readers of the problems associated with selective outcome reporting. Work published in 2010 surveyed 283 randomly selected Cochrane reviews and their 2486 included trials. It found that 157/283 (55%) Cochrane reviews did not include complete data for their primary outcomes. 155/2486 (6%) of included trials had measured the primary outcome of the Cochrane review which they had been included in, but then neglected to report it (121). This highlights the significant prevalence of this problem and the effect it has on systematic review and meta-analysis.

3.3 The COMET Initiative

The COMET initiative (Core Outcome Measures in Effectiveness Trials) provides a framework for those developing core outcome sets for all trials examining a specific condition (116). In addition to providing consistent design, trials will include outcomes that reflect real-life of patients, this also makes it easier to include data into meta-analyses. This will mean that results from more trials can be included and a more accurate consensus may be reached.

When the search term ‘cystic fibrosis’ is used to search the COMET database, two papers are identified that report discussions regarding core outcome measures for cystic fibrosis at previous workshops/conferences (122, 123). There is a paucity of guidance for those conducting trials in CF and these discussions make little specific referral to pre-school children aged 0-5. There are relatively few trials in pscwCF, and it is especially important to make sure that those trials provide optimal information using outcome measures that equate to long term wellbeing.

For the second part of my MPhil project, I will review outcomes which are reported in trials in this age group with the aim of informing the process of determining the most useful outcomes for these trials.

A brief review regarding outcomes in multiple respiratory diseases, including CF was performed in 2010 (124). It describes several points for 0-6 year olds but requires more detail and an update is necessary due to new trials being performed since 2010. This review makes the important point that surrogate outcomes do not equal a direct clinical benefit to patients and may not equal a change in a pragmatic outcome. It found that in general, trials in CF included quality of life, pulmonary function, rates of pulmonary exacerbation, growth, microbiology, inflammatory markers, nasal potential difference and radiological imaging, with the target age group influencing which outcomes are selected. This review also points out that in pscwCF, outcomes are particularly limited due to difficulty with spirometry, imaging resolution not being able to pick up the usually very small changes to airways at this age, difficulty collecting sputum samples and the fact that the typically used CFQ-R quality of life questionnaire is not applicable to pscwCF. It finishes by saying that during the next 10 years from when it was written, trials of interventions which use improved outcome measures will lead to greater benefits for these children thanks to earlier identification and treatment of disease (124).

OMERACT (Outcome Measures in Rheumatology), has promoted the use of core outcome sets for rheumatology trials for twenty years (125). Earlier still, in 1979, the WHO produced a handbook for how cancer trials should report results (126). COMET was launched in Liverpool in 2010 (125). Although numerous specialities acknowledge the value that core outcome sets can provide, there is a lack at any age group in the field of cystic fibrosis. A core outcome set taskforce for CF (COST-CF) headed by Professor Alan Smyth in Nottingham have registered with COMET (127), but efforts to fund this project are yet to be successful.

3.4 The utility of core outcome sets

Asthma is an example of where considerable work has been done to determine the most important outcomes, both for children, young people and adults (128, 129). Challenges were identified during the development process for this COS included encouraging people to consider the idea that although you can measure a particular endpoint, it doesn't always mean that it is useful to do so; as numerous stakeholders considered the idea that if there was a means to measure an endpoint, it may as well be measured. Another challenge in

this work which aims to provide as much value to as many stakeholders as possible was the different approaches and reasons that stakeholders had for being involved in research trials and the difficulty in ensuring a COS satisfies them all: patients may want to be involved to see if the next new therapy makes a difference to their wellbeing, pharmaceutical companies want to ensure their drug is safe and effective to take to market, commissioners want to learn if an intervention is cost effective and so on. These challenges are important to consider for the creation of a future COS in CF. Further work is also currently being undertaken to further refine core outcomes for asthma, accounting for factors such as severity of asthma. Examples of such include the coreASTHMA project and the PERN asthma working group (130, 131).

Another good example of work to develop core outcome sets is for rheumatoid arthritis, with work first going back as far the 1980s and still ongoing today to update and improve core outcomes to keep pace with the standards of research (132-134). Work in this field has included many stakeholders, including a lot of focus on patient perspective which has been considered a very important component in determining core outcomes (135, 136).

3.5 Development of a core outcome set

There is a standard methodology agreed upon for the process of developing a core outcome set (116). It should involve engaging with different stakeholders, for example health professionals, policy makers and the people who use these interventions, as well as their parents or carers. The decision on which stakeholders should be involved for each COS set will be determined by discussion about the scope of each COS, existing knowledge on the topic concerned and what is feasible (117). There are examples showing that patients aren't often involved in these discussions, but when they were involved, they came up with outcomes which the other stakeholders had not considered. Good examples again come from the field of rheumatology; at a patient perspective workshop as part of an OMERACT meeting, they found that more emphasis needed placing on subjective experience of people living with rheumatoid arthritis including sense of wellbeing, disrupted sleep and fatigue as well as using less jargon and continuing to make patients an important component in outcomes research (137). In another publication, interviews with 23 people with rheumatoid arthritis identified 60 outcomes which these people sought from their treatment, in addition to the outcomes already commonly considered in trials of treatments for this condition (138).

There is also mention that as well as setting out what should be measured by trials, there should also be a validated tool to measure these where possible. An illustrative example of this which has previously been used by members of the COMET team (117) is a systematic review regarding breast reconstruction which found that 906 different outcomes were measured, but only 20% of these outcomes were measured using a validated tool (139, 140). An example of an outcome in CF that is difficult to validly quantify is pulmonary exacerbations, which can incorporate a degree of subjectivity as to how they affect individual people with CF rather than having a valid measure of severity that is reproducible across all people with CF.

The Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) is a Dutch body with the aim to help assess the validity of measurement tools and also select a tool which has already been validated to measure a given outcome (141). There is also another initiative called PROMIS (Patient-Reported Outcomes Measurement Information System) which provides validated measurement tools for patient reported outcomes relating to physical, mental and social health in chronic diseases. They also include tools specific to children and parent proxy tools including measures with the potential to be applied to pscwCF such as life satisfaction, physical activity and peer & family relationships (142).

A discussion on the value of core outcomes and their valid measurement for cystic fibrosis research was published in 1994. This discussion included the importance of determining a validated measure of outcomes for multiple parameters in young children aged 0-5. These parameters included pulmonary function testing, a validated disease severity score for young children, reliable radiological assessment, quality of life and wellbeing (122). Our work is different to this as it exclusively examines preschool children with CF and we further build upon its work by comprehensively recording the outcomes reported by the protocol, methods and results of Cochrane systematic reviews and their included trials in pre-school children.

A starting point on the journey to develop a COS for pscwCF is a review to record what outcomes have currently been measured in this age group.

The next steps of the COMET process would involve engaging with stakeholders through both discussions and a Delphi survey. A list of possible outcomes is devised, and stakeholders are asked to select which of these is important to them and also suggest any which may have been missed (round 1). The responses are collated, and a summary is sent

back to each respondent, along with a reminder of their round 1 responses. After reviewing the summary, they then decide whether they want to change their responses (round 2). The results are collated again by the researchers, who can decide they have adequate information or can continue asking respondents for rounds of responses. Upon completion of the survey part, respondents are invited to a group discussion about the results to again help refine what are the best outcomes to measure. A report is then produced on what the experts and stakeholders consider to be the most important outcomes (143).

3.6 Possible difficulties for core outcomes

Some pragmatic measures in this age group may be difficult to use as a reliable measure of how a pre-school child is managing with their CF. A pragmatic measure is one which directly shows the effect of an intervention on the person and their family. Some examples of pragmatic outcomes that may be useful in this age group are the frequency of antibiotics, number of hospitalisations, and parent reported outcomes (typically based on the symptoms of their child, but these measures need appropriately validating).

Surrogate measures can provide valuable information and are often used. Surrogate measures are an investigation or physical sign which can be used as a substitute for a more meaningful measure of a person's quality of life, survival or functional status, and are sometimes referred to as biomarkers. They should predict the effect of the intervention (144). An example of a surrogate measure would be sweat chloride, infant pulmonary function tests or lung clearance index.

A secondary analysis of the ISIS study (Infant Study of Inhaled Saline) looked at the use of infant pulmonary function testing as endpoints in an RCT of infants with CF. It concluded that pulmonary function tests in infants were not appropriate primary endpoints due to the difficulty of obtaining acceptably useful data and the near-normal results they provided in a young age group where significant airway damage may not have occurred. Stated that more modern measures such as that of LCI may be better at giving a picture of pulmonary status in this group, but the fact that its results differ to those provided by infant pulmonary function tests, in that one tool may measure as normal whereas the other measures as abnormal (or vice versa) shows they may reflect different parts of pathophysiological processes occurring in the lungs, and are not analogous to one another (145). Imaging may not be sensitive enough to detect small changes which may have developed. It is impossible to produce a good sputum sample in most pscwCF and oropharyngeal swabs are a less reliable test (124).

A commentary from 2007 discusses the difficulties experienced when collating information from multiple trials for systematic reviews, such as measurement of a similar endpoint using different tools. It highlights a review of over 2000 trials for treatments of schizophrenia. They identified over 600 different interventions, but interestingly found an even greater number of 640 different mental health scoring tools from these trials. Having such a large number of different measuring tools for the same or similar outcomes makes it difficult to select the most valid and reliable tool. The same 2007 commentary also points out the importance of how a COS can help overcome selective outcome reporting (a sentiment also shared by COMET) (121, 146, 147).

4. Cochrane systematic review

4.1 Background

This work represents a substantial update of a previously published systematic review concerning correctors (99). The use of these medicines was examined in people with CF with at least one class II variant and they were also tested as single agents (monotherapy) and some as part of a combination of a corrector and a potentiator (discussed above), this was known as dual combination therapy.

The previous version found that correctors, when used in monotherapy for class II variants showed no or little benefit versus placebo in the outcomes measured in the review. Dual combination showed modest improvement in some measures significant adverse events were reported for lumacaftor/ivacaftor (99).

The area of novel CFTR modulating therapies is changing rapidly, and it is important to incorporate new data when available to inform up to date decision making such as health technology assessments. New trial data had been released since the latest version and therefore an update is valuable. As this is an update, the rationale for the systematic review and eligibility criteria were unchanged.

4.1.1 Description of the intervention

We have learnt more over recent years as to how the different *CFTR* variant classes affect the synthesis, processing and trafficking pathway of the *CFTR* protein, and therefore where we can intervene to aid the presence of a functional protein at the cell surface. As class II variants lead to defects in folding and intracellular trafficking. The intervention to target this problem must therefore correct or mask the folding of the protein and are hence known as 'correctors'. Correctors are small molecule drugs which were discovered by either the testing of compounds in known medications, plants, foodstuffs etc. already known to have an effect on *CFTR* or other ion channels; or by high throughput screening which involves testing many small molecule compounds to see if they have an effect on *CFTR* function (148).

4.1.2 How the intervention might work

The aim of correctors is to facilitate the *CFTR* protein to overcome its class II trafficking defect. We do not know for certain their mechanisms of action, but it is thought correctors help to mask the folding defect so that the ion channel represents a *CFTR* not affected by a CF causing variant (a 'normal' or wild type *CFTR*), allowing it to reach the cell surface

without being broken down. Once at the cell surface this class II *CFTR* may still have reduced function and so a potentiator medication may also be required to increase the probability that the chloride channels will be open (149).

4.1.3 Why it is important to do this review

Correctors have only been in widespread use for a short number of years and new correctors are being synthesised and tested all the time, with results of new trials being published frequently. It is therefore important that this systematic review keeps pace with the evidence to have an up to date assessment of the benefits and harms of these drugs over a longer time period. As there is often a significant cost associated with these medicines it is important for such information to be available to stakeholders and funding bodies (99).

4.1.4 Objectives

To assess the efficacy of CFTR corrector medications on outcomes considered as clinically important, as well as their potential harms and adverse effects in children and adults with CF and at least one copy of a class II *CFTR* variant.

4.2 Methods for Cochrane systematic review

4.2.1 Identifying potentially eligible studies

The data search was carried out by an information specialist in the Cochrane Cystic Fibrosis & Genetic Disorders (CFGD) group. The information specialist searched the Cystic Fibrosis Trials Register, maintained by the Cochrane CFGD group to keep a record of all clinical trials conducted in the field of CF. This is compiled with results from CENTRAL, the Cochrane Central Register of Controlled Trials. The register also compiles search results of MEDLINE (conducted every quarter) and search results of Embase to 1995. The terms used to search this register was 'drugs that correct defects in CFTR transcription, translation or processing', with which applicable studies have been tagged in the register.

Additionally, hand searching of the journals *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis* is performed. Clinical trials registers were also searched as another means of ensuring no eligible trials were missed. This was also performed by the information specialist, according to the previously determined protocol. The clinical trial registers which were searched were:

- The European Medicines agency; clinicaltrialsregister.eu
- The US National Institute of health; clinicaltrials.gov
- The World Health Organisation; who.int/ctrp/en

All of these trial registers were searched with the terms: Cystic fibrosis AND (VX OR corrector). VX refers to the abbreviation used by the pharmaceutical company Vertex to test their new experimental drugs e.g. VX-445.

Also, to identify further studies which may be eligible, bibliographies of already included studies were checked, as well as contacting their authors and known leaders in CF research and pharmaceutical companies who are known to be working on the development of *CFTR* correctors. This was performed by both the information specialist and myself (JM), according to the already determined protocol.

Finally, in order to identify as yet unpublished work, the abstract books of three large CF conferences were searched by the information specialist, according to the protocol. These conferences are: The International Cystic Fibrosis Conference, The European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. Once the search identified

potentially eligible papers, we sought the abstracts and full versions of the citations, where available.

4.2.2 Assessing eligibility

Cochrane requires eligibility assessments and data extraction for trials to be performed independently by at least two people. Therefore, two of the team (JM & IS) used the criteria provided in the Cochrane study selection, quality assessment and data extraction form to identify those studies which were eligible. Those criteria were:

- Appropriate study design- We included parallel design RCTs. We did not include cross-over studies as correctors address the underlying defect and would alter the course of disease if effective, having an impact on results.
- Relevant participants- does the included study population fit with your criteria? We included participants of any age and any level of disease severity. They should have one or two class II *CFTR* variants.
- Relevant interventions- is the study looking at an appropriate intervention? We were looking specifically for corrector medications to overcome F508del variants affecting *CFTR*.
- Relevant outcomes- does the study measure/report on outcomes which your review is including? Our outcomes of interest are listed below. However, if trials of a drug considered to be a corrector did not report outcomes stated in the review, we still considered whether it had any valuable information.

If the answer was yes to all of the above criteria, the study was eligible for inclusion in the Cochrane review. If the two people assessing eligibility found they had disagreements over eligibility, they discussed them to try and reach a consensus. If necessary, a third team member would arbitrate.

In the case of only abstracts being identified for eligible studies, which stated further data would be available soon, or not all data was thoroughly included, we contacted authors for further information regarding the design, methodology and results of the survey. This was performed according to standard Cochrane methodology, which is adhered to in the previously determined protocol, but is performed on newly identified citations from a new data search for this update.

4.2.3 Outcomes recorded

These outcomes were determined by reviewing similar interventions in cystic fibrosis. There was also discussion between multiple stakeholders, including experts in the field, trial investigators, other clinicians and patients/families. These processes then led to eliciting what outcomes are most often of interest and value to multiple stakeholders. The outcomes were not changed in this latest update of the review and therefore I (JM) was not involved in determining the outcomes to be examined.

4.2.3.1 Primary outcomes:

1. Survival
2. Quality of life (which used a validated quantitative measure, for example the Cystic Fibrosis Questionnaire- Revised (CFQ-R) (150))
    a. Total quality of life score
    b. Any sub-domains which may have been reported
3. Physiological measures of lung function- litres or percent predicted according to demographics of the patient.
    a. Relative change from baseline of FEV_1 (Forced expiratory volume after one second)
    b. Absolute change from baseline in FEV_1 values
    c. Absolute values and change from baseline for FVC (Forced vital capacity)
    d. Lung clearance index
    e. Other relevant measures of lung function

4.2.3.2 Secondary outcomes:

1. Adverse effects- We classified adverse events according to:
    a. Mild- therapy did not need to be stopped.
    b. Moderate- therapy stops, then adverse effect stops
    c. Severe- adverse effect still persists after stopping therapy, or an effect which is life threatening or debilitating.
    d. Other adverse event due to the experimental therapy which cannot be classified by the above categories.
2. Hospitalisation
    a. Number of days spent in hospital
    b. Number of admissions to hospital
    c. Time to next hospital admission

3. Measures of attendance for work or school (for example, number of days missed due to illness)
4. Use of extra antibiotics (total number of antibiotic courses, or time to next antibiotic course)- incorporating the occurrence of pulmonary exacerbations.
    a. Oral antibiotics
    b. Intravenous antibiotics
    c. Inhaled antibiotics
5. *CFTR* function- Change from baseline of sweat chloride level
6. Radiological scoring system for measuring lung disease (any score)
    a. Chest X-ray scores
    b. Computerised tomography scores
7. Respiratory pathogen acquisition
    a. *Pseudomonas (P.) aeruginosa*
    b. *Staphylococcus (S.) aureus*
    c. *Haemophilus (H.) influenzae*
    d. Other respiratory pathogens clinically relevant to cystic fibrosis patients
8. Eradication of respiratory pathogens
    a. P. aeruginosa
    b. S. aureus
    c. H. Influenzae
    d. Other respiratory pathogens clinically relevant to cystic fibrosis patients
9. Measures of nutrition & growth- relative change from baseline, including z scores or centiles
    a. Weight
    b. Body Mass Index (BMI)
    c. Height

4.2.4 Data extraction

Two authors (JM & IS) performed data extraction for the newly eligible studies, if there was disagreement a third author arbitrated where necessary (KWS).

For this update, a new data extraction spreadsheet was created by JM, based on that provided by the Cochrane Collaboration. Due to the complex design of some of the trials however, adaptations were required to incorporate the multiple measures taken at different time points, for a range of doses and different combinations of *CFTR* mutations. Some trials even included different versions of the same molecule, for example Ivacaftor and VX-561, a deuterated form of Ivacaftor which is considered more stable and therefore taken once per day as opposed to the usual twice per day (151, 152). An example of this new data extraction sheet can be found in the appendix.

Eligible papers were read and outcomes from the list above extracted and input to the data extraction form. Data was classified according to timeframe: immediate (up to and including one month), short term (over one month to six months) or long term (over six months).

4.2.5 Risk of bias

Two authors (JM & IS) were required to assess the risk of bias in included trials. Cochrane provide a risk of bias tool and a chapter in their handbook to provide guidance on the domains to consider when assessing a study's risk of bias (107, 153). These domains are:

- Procedure for randomisation- what method was used in order to create the process of randomising patients? Was it done by someone independent of the study itself? And will it produce sufficiently comparable groups? This is examining selection bias.
- Allocation concealment- Was it possible for study personnel or patients to determine the allocation sequence before or during enrolment? This is also looking into selection bias. The author should find out the method used to conceal allocation.
- Blinding of the intervention from participants, clinicians and other study personnel- What methods were used to mask which intervention a participant was given? Were these efforts effective? This examines performance bias.
- Blinding of outcome assessment- What steps were taken to prevent those people who are measuring and analysing the outcomes of interest in the study, from

learning which intervention a patient received? Was this blinding effective? This is an example of detection bias.

- Incomplete outcome data- Was every patient who was originally enrolled and randomised then accounted for as part of the results for each outcome? Are any patients who were excluded or dropped out accounted for, along with reasons explaining their attrition? This is examining attrition bias.
- Selective reporting- were all outcomes that were stated in the protocol/methods then reported in the results? If there were any outcomes which were not measure, were there any reasons why? If yes, they should be stated transparently. This is looking at reporting bias.
- Other bias- an opportunity for review authors to identify any other concerns regarding bias which the above criteria don't cover.

4.2.5.1 The different domains of bias

The Cochrane risk of bias assessment tool looks for the risk of multiple domains of bias. These domains are:

- Selection bias- when a cohort in a study has a systematic difference (other than the intervention or exposure) from the population of interest. This can lead to a systematic difference in measured results. An example could be an intervention intended to be used mainly for elderly people being tested in a cohort of young adults.
- Reporting bias- this can occur when the reporting of results is influenced by other factors. It comprises several sub-categories (154):
    - **Publication bias**- work is more or less likely to be published depending on the findings e.g. very positive or highly significant. This can also lead to:
    - Time lag bias- if work is high profile or produces very positive or significant results, it is more likely to be published quicker.
    - Multiple/duplicate publication bias- depending on results, work may be submitted/published multiple times to different journals/conferences etc.
    - Location bias- depending on results, work may be published in journals which are easier/more difficult to find or access, or with different impact factors.
    - Citation bias- despite being relevant, work may not be cited if its results don't fit with a point that is being made.
    - Language- work is more likely to be published in English if it shows favourable results.
    - **Outcome reporting bias**- some studies may not fully report the results of all the outcomes which they stated in protocol or methodology.

- Performance bias- can occur when the researcher or the participant is aware of if they have been allocated to intervention or control. It can lead to differences between care given to participants and can lead to the true treatment effect of the intervention being disrupted or masked.
- Detection bias- this occurs due to differences in how the outcome of interest differs e.g. different people or using a different piece of equipment to measure an outcome.
- Attrition bias- this can happen when there is incomplete outcome data for all participants due to participants pulling out of trials or being lost to follow up. This attrition of patients may occur unequally between the intervention and control groups and there may be systematic differences between those who are more likely to drop out and those more likely to remain in the trial, for example participants who are more severely ill may be more likely to drop out, leaving the more well participants to continue in a cohort which is now not fully representative.

Publication bias can occur if a trial finds negative results and therefore decides to withhold from publishing them (155). This can have the consequence of making the consensus of literature inaccurate from the true answers it should hopefully be able to give us and may shape the direction of future work on a sub-optimal course.

To check for the possibility of publication bias, one of the team members (a statistician, SJN) would have aided in the construction of a funnel plot, which plots the number of patients in a given study, against a measure of treatment effect. Once this was plotted for every included study, we would have checked if the funnel plot is symmetrical or not. If it was asymmetrical, this may be due to publication bias. However, it should be noted that there are other causes of asymmetrical plots: methodology of the studies, small sample sizes and chance can all have an effect. In order to create a meaningful funnel plot, you require at least 10 trials to be included in your review.

Funnel plots often show standard error (y axis) as a measure of study power, the scale of which is inverted. This means the more powerful studies with smaller standard error are at the top of the scale. This is plotted against a measure such as mean difference or odds ratio (x axis). The included studies are plotted on this graph and should spread out and, assuming no bias is present, 95% of studies should be included within a funnel extending from zero at the top of the inverted y axis scale, to 1.96 standard errors either side of the scale on the x axis (156).

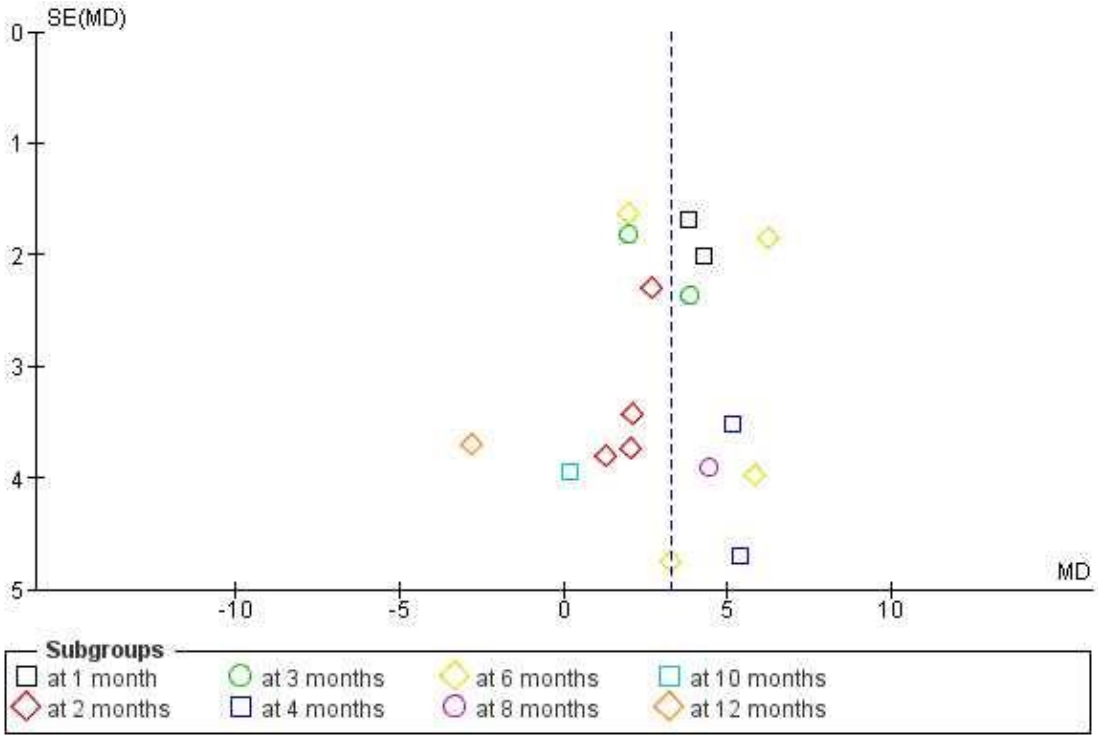

***Figure 5**: An example of a funnel plot comparing relative change in % predicted FEV_1 for azithromycin versus placebo. From Macrolide antibiotics for cystic fibrosis. From Southern KW et al. 2012 (110)*

4.2.6 Measures of treatment effect

Continuous outcomes were measured by first finding their mean change from baseline and their standard deviations. Where necessary we calculated mean change ourselves, providing that we had measures for the same value at baseline and the end for the studies. These values can then be used to find a mean difference with 95% confidence intervals.

For binary outcomes, overall treatment effect was calculated using a pooled odds ratio with 95% confidence intervals.

For time to event outcomes, we used hazard ratios and their 95% confidence intervals.

Outcomes that were reported by multiple studies were put into meta-analyses to find an overall representation of treatment effect. Forest plots were drawn to illustrate magnitude of effect and examine for consistency (homogeneity) of results.

4.2.7 Heterogeneity

No two studies are the same. The differences between them are collectively termed heterogeneity, of which there are several types (157).

Clinical heterogeneity is the differences that exist between the participants of the study; their age, their sex or medical history are possible examples.

Methodological heterogeneity is where there are variations in the design of the study e.g. length of test period, parallel vs. crossover. It can also relate to differences between risks of bias, including the different sub-domains (mentioned above).

Statistical heterogeneity is any differences between the effects that different trials are trying to measure. This is particularly notable during meta-analysis, where we must ask- "Are these effects similar enough for us to combine as part of the same analysis? Are they measuring the same thing?" Both clinical and methodological heterogeneity can lead to statistical heterogeneity. These reasons are why when work such as systematic reviews & meta-analyses mention heterogeneity, they are most often mainly referring to statistical heterogeneity (157).

There are several ways to look for possible heterogeneity. One way to is to examine confidence intervals for values of the same effect between different studies; if there is little overlap, this may raise suspicion of heterogeneity. You can also use the Chi^2 test which can give information about whether differences between results are due to chance or not. A Chi^2 statistic that is large compared to its degree of freedom can suggest the variation in

effect measures is not just due to chance. The method that is commonly used in Cochrane reviews is the I^2 statistic, which builds upon the Chi^2 statistic using the following equation (158, 159):

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

In this equation, Q is the Chi^2 statistic and df is its degrees of freedom.

The output is a percentage value, which can be interpreted as such (157):

0-40%: less likely to be important heterogeneity.

30-60%: may be some moderate heterogeneity.

50-90%: may substantial heterogeneity.

75-100%: heterogeneity is considerable.

The value of the I^2 statistic is limited to the strength of the evidence for heterogeneity such as the confidence interval for I^2 or the P value of its respective Chi^2 test (157).

We planned that in the eventuality that heterogeneity between studies was found, we would perform subgroup analyses to account for potential confounders. The confounders that would be accounted for are: age (children under 18 vs. adults age 18 or over), gender and class of mutation. Subgroup analyses could only be performed if there were at least 10 studies.

4.2.8 Sensitivity analysis

Sensitivity analysis is a method of attempting to find how uncertainty in a given information source affects the overall (un)certainty of your meta-analysis. It is done by performing the same meta-analysis; once where you include all applicable studies, and a second time when you've excluded those studies with a high risk of bias. The two meta-analyses are then compared to see if there is any impact on results from the potential biases.

4.3 Results of Cochrane systematic review

4.3.1 Context of this result section

This work represents a substantial update of the first review published in 2018. For this review I have re-assessed outcome data from the first review and have included new data from four studies that are newly available since the first review. These studies examined a monotherapy (Horsley (160)) and various triple combination therapies (Davies a, Davies b (152) and Keating (151)).

This work will critically appraise the new studies and present outcomes in the context of the first review.

4.3.2 Study selection

4.3.2.1 Included studies

Monotherapy

Eight studies were included, with a total of 344 participants (160-167). The drugs which were examined in monotherapy were sodium phenylbutyrate (4BPA), N6022, 8-cyclopentyl-1, 3-dipropylxanthine (CPX), cavosonstat and lumacaftor. There was one newly added study (Horsley (160)) which compared FDL169 at doses of 400 mg (n = 6), 600 mg (n = 6) and 800 mg (n = 8), each taken three times daily, versus placebo (n = 7) for 28 days.

Dual combination therapy

Six studies were included in the previous edition of this systematic review, they included a total of 1898 participants (100, 161, 168-170) (the TRAFFIC and TRANSPORT studies are included as part of a single reference). An additional study (PROGRESS) provided safety data for the analysis (171); despite progress being open label continuation of TRAFFIC and TRANSPORT, it was felt that the safety data it provided was important to be included and so an exception was made to include it. Its efficacy data was not included.

Four studies compared lumacaftor-ivacaftor versus placebo in 1376 participants (161, 168, 170). Two studies compared tezacaftor-ivacaftor versus placebo in 522 patients (100, 169). No new studies of dual combination therapies were identified by this update.

Triple combination therapy

Three newly identified triple combination studies consisted of one phase 1 study and two phase 2 studies. All were of parallel design. The studies included a total of 255 participants.

Their sample sizes consisted of 12 for Davies 2018 (a) (152), 121 for Davies 2018 (b) (152) and 123 for Keating 2018 (151). The Davies 2018 phase 1 and 2 studies- 'a and b', are published as part of the same paper (152).

Duration of these studies ranged from 14 days (Davies 2018 (a)) to 4 weeks (Davies 2018 (b) & Keating 2018 (151)).

All studies were multi-centre. Full texts were available for all 3 of the new triple combination studies.

The two Davies studies tested VX-659-tezacaftor-ivacaftor combination therapy. The phase 1 study (a) compared a single dose level of 120 mg VX-659 taken twice daily in combination with tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily for 14 days in participants with a compound heterozygous F508del/MF genotype (152). The following phase 2 study, Davies (b), tested VX-659 in ascending once daily doses of 80 mg, 240 mg & 400 mg in participants with an F508del/MF genotype for 4 weeks. In a separate group of people with this same genotype, investigators studied the regimen of VX-659 400 mg once daily plus tezacaftor 100 mg once daily plus VX-561 (deuterated ivacaftor) 150 mg once daily versus placebo for 4 weeks. Davies (b) also included a group of patients with F508del/F508del genotypes who took VX-659 400 mg plus tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily versus the control of tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily, which the study considered as the standard of care for people with CF who have this genotype (152).

Keating, a phase 2 study tested VX-445-tezacaftor-ivacaftor combination therapy in ascending doses of 50 mg, 100 mg and 200 mg once daily of VX-445 in triple combination with tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily in participants with an F508del/MF genotype. In another group of participants with the F508del/MF genotype, the study tested VX-445 200 mg once daily plus tezacaftor 100 mg once daily and VX-561 (deuterated ivacaftor) 150 mg once daily. Additionally, in a group of patients homozygous for F508del, they also tested VX-445 200 mg once daily plus tezacaftor 100 mg once daily and ivacaftor 150 mg twice daily (151).

4.3.2.2 Excluded studies

From this latest search, 5 references relating to 3 studies were excluded. 1 reference related to EXTEND , an open label extension of the already included EVOLVE tezacaftor-ivacaftor dual combination trial (172). 2 references (173, 174) related to a crossover study of tezacaftor-ivacaftor in people with CF who have an F508del/residual function genotype (175). 2 references related to a study of a drug called QR-010, an antisense-oligonucleotide which we did not consider to be a corrector for F508del *CFTR* variants (176, 177).

The first version of this review had excluded 11 studies from its literature search. Six were excluded for being a crossover design (175, 178-182), two were single assignment studies (183, 184), one was not randomised (185), one was a pre-clinical lab based study (186) and one studied general gene therapy and not variant specific therapies (187).

4.3.2.3 Ongoing studies

Following results from this latest data search, 17 studies are listed as ongoing.

7 studies are examining monotherapy. 2 of which are studying GLPG2222 (188-191). 2 are studying PTI-428 (NCT02718495, NCT03258424). One study is examining roscovitine (192). Another study is looking at GPBA (NCT02323100) and one study is examining PTI-801 alone and in combination with PTI-428 (193).

4 ongoing studies are looking at dual combination therapy. 4 are comparing tezacaftor-ivacaftor, 3 in participants with F508del/F508del genotypes and 1 in participants with a genotype of F508del/variant responsive to ivacaftor.

3 ongoing trials are studying triple therapy combination. One is examining VX-152-tezacaftor-ivacaftor (NCT02951195). One is studying VX-445-tezacaftor-ivacaftor in people with CF with either F508del/F508del or F508del/MF genotypes as well as people without CF (NCT03227471). A third study is evaluating the addition of cavosonstat to people with CF with the F508del/F508del genotype who are already taking lumacaftor-ivacaftor (NCT02589236).

A more detailed summary of ongoing studies is available in the appendix.

4.3.3 Study quality

Below is a table summarising the results of risk of bias assessments for the newly added studies from this update. Risk of bias assessments of all remaining included studies can be found in the appendix.

For table 1, green indicates a low risk of bias, yellow an uncertain risk of bias and red a high risk of bias (none shown). Please see tables 2-5 below for a breakdown and reasoning on why each domain has been judged to have its respective risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Davies 2018 (a)							
Davies 2018 (b)							
Horsley 2017							
Keating 2018							

***Table 1**: Risk of bias summary of newly included studies from latest update of Cochrane systematic review.*

Bias domain	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that participants are randomised but does not state the method by which they are randomised.
Allocation concealment (selection bias)	Unclear risk	Does not state methods of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Does not state who was and was not blinded during the study.
Blinding of outcome assessment (detection bias)	Unclear risk	Does not state how outcome assessors were blinded during study.
Incomplete outcome data (attrition bias)	Low risk	All participants who were randomised are accounted for.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods are reported in the results.
Other bias	Unclear risk	As the only information available was as part of a poster and a full detailed publication has not been published, it is difficult to say with any certainty whether there are other sources of bias in the process of this study.

***Table 2**: Risk of bias table for Horsley 2017.*

Bias domain	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list made by Vertex Biostatistics or a randomisation vendor. Final list reviewed and approved by a designated unblinded statistician who is independent of the study team. Interactive web response system used to assign participants to treatment.
Allocation concealment (selection bias)	Low risk	Random allocation independent of study team. Use of interactive web response system.
Blinding of participants and personnel (performance bias)	Low risk	All participants, site personnel and Vertex study team were blinded to allocation. Protocol sets out conditions when blinding could/should be broken.
Blinding of outcome assessment (detection bias)	Unclear risk	All authors were only allowed access to study data after they were unblinded. No mention is made of other outcome assessors (e.g. clinicians who were not authors but were involved in seeing participants and measuring outcomes of interest) and whether there was a possibility of them knowing allocated intervention.
Incomplete outcome data (attrition bias)	Low risk	All participants who were randomised are accounted for.
Selective reporting (reporting bias)	Unclear risk	States in methods that it would measure 12-lead ECG and vital signs, though these may have been measured, they are not stated in results or supplement regardless of if they were unremarkable or not.
Other bias	Low risk	Different groups of participants are balanced in baseline characteristics, no statistically significant difference between them. Detail in paper and its supplement does not cause any concern for other sources of bias not previously mentioned.

***Table 3**: Risk of bias table for Davies 2018 (a).*

Bias domain	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code made by Vertex Biometrics or a 'qualified randomisation vendor'. Randomisation stratified by ppFEV$_1$ being less than or equal to/greater than 70%.
Allocation concealment (selection bias)	Low risk	Use of interactive web response system to allocate participants to groups.
Blinding of participants and personnel (performance bias)	Low risk	All participants, site personnel and Vertex study team were blinded to allocation. Protocol sets out conditions when blinding could/should be broken.
Blinding of outcome assessment (detection bias)	Unclear risk	All authors were only allowed access to trial data after they were unblinded. No mention is made of other outcome assessors (e.g. clinicians who weren't authors but were involved in seeing participating patients and measuring outcomes of interest) and whether there was a possibility of them knowing allocated intervention.
Incomplete outcome data (attrition bias)	Low risk	All patients who were randomised are accounted for.
Selective reporting (reporting bias)	Unclear risk	States in methods that it would measure 12 lead ECG and vital signs, though these may have been measured, they are not stated in result or supplement regardless of if they were unremarkable or not.
Other bias	Low risk	Different groups of participants are balanced in baseline characteristics, no statistically significant difference between them. Detail in paper and its supplement does not cause any concern for other sources of bias not previously mentioned.

Table 4: *Risk of bias table for Davies 2018 (b)*

Bias domain	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code made by Vertex Biostatistics or a 'qualified randomisation vendor'. Randomisation stratified by FEV_1 % predicted (less than or equal to 70% versus greater than 70%).
Allocation concealment (selection bias)	Low risk	Use of interactive web response system for allocation.
Blinding of participants and personnel (performance bias)	Low risk	All participants, site personnel and Vertex study team related to the study were blinded. A clear statement on when unblinding is necessary/permitted is provided in the protocol.
Blinding of outcome assessment (detection bias)	Unclear risk	All authors were only allowed access to study data after they were unblinded. No mention is made of other outcome assessors (e.g. clinicians who were not authors but were involved in seeing participants and measuring outcomes of interest) and whether there was a possibility of them knowing allocated intervention.
Incomplete outcome data (attrition bias)	Low risk	All participants who were randomised are accounted for.
Selective reporting (reporting bias)	Unclear risk	States in methods that it would measure 12-lead ECG and vital signs, though these may have been measured, they are not stated in results or supplement regardless of if they were unremarkable or not.
Other bias	Low risk	Different groups of participants are balanced in baseline characteristics, no statistically significant difference between them. Detail in paper and its supplement does not cause any concern for other sources of bias not previously mentioned.

Table 5: *Risk of bias table for Keating 2018*

4.3.4 Effects of interventions

4.3.4.1 Monotherapy

Primary outcomes

1. **Survival:**

None of the studies reported any deaths.

2. **Quality of life:**

a. **Total QoL score**

No studies reported upon this outcome.

b. **Different QoL sub-domains**

Data were available for effects lumacaftor and cavosonstat on QoL sub-domains of the CFQ-R quality of life score for the immediate time-frame (up to 1 month). No significant improvements were seen between intervention and placebo across all domains for both drugs and lumacaftor lead to a statistically significant decrease in CFQ-R scores for the role domain (25 mg), respiratory (25 mg & 50 mg), eating, health perceptions and treatment burden domains (50 mg) (162, 164).

Horsley reported FDL169 led to a change from baseline at 28 days for the CFQ-R respiratory domain. This favoured the 400 mg group (n = 6) compared to placebo, MD 5.09 (95% CI -2.72 to 12.90); there was no difference between the 600 mg group (n = 6) and placebo, MD -4.33 (95% CI -12.01 to 3.35); and favoured the 800 mg group (n = 8) over placebo, MD 8.84 (95% CI 1.40 to 16.28) (160).

3. **Physiological measures of lung function**
   a. **FEV_1 relative change from baseline:**

Data for this were available for lumacaftor, cavosonstat (FEV_1 relative change and absolute values and FVC) and N6022 (FEV_1 relative change). No statistically significant difference was observed versus placebo for any of these medications (162-164).

b. FEV_1 (absolute values)

Data for this were available for lumacaftor and cavosonstat, which led to no statistically significant difference in FEV_1 absolute change (162, 164). Data was also available for FDL169. This study reported the absolute change from baseline in FEV_1 % predicted at day 28; there was a greater increase in the 400 mg group than placebo, MD 4.68 (95% CI 0.12 to 9.24) but no difference between the 600 mg group and placebo, MD 2.80 (95% CI -1.82 to 7.42) or between the 800 mg group and placebo, MD 0.68 (95% CI -3.80 to 5.16) (160).

c. FVC

This outcome was reported for Cavosonstat, which led to no statistically significant changes in FVC versus placebo (164).

d. LCI

Not reported by any study.

e. Other relevant measures of lung function

Secondary outcomes

1. **Adverse events:**

Lumacaftor- No significant difference was observed between lumacaftor and placebo in the number of participants experiencing adverse effects at day 14, and the severity of these effects (161, 162).

Cavosonstat- all adverse events were found to be mild or moderate and there was no significant difference between cavosonstat and placebo in the occurrence and severity of adverse events (164).

N6022- no significant difference was reported in the occurrence and severity of adverse events between N6022 and placebo (163).

CPX- no significant difference was reported in the occurrence and severity of adverse events between CPX and placebo (165).

4BPA- No statistically significant difference was reported in the occurrence and severity of adverse events between 4BPA and placebo. This was the case for both the pilot and phase 2 studies of this medication (166, 167).

FDL169- This study reported the number of participants experiencing at least one adverse event, and the number of 'serious' adverse events, AEs were not categorised under mild, moderate or severe. No statistically significant difference was found in the number of participants experiencing at least one adverse event between any tested dose level of FDL169 and placebo; for the 400 mg group, OR 6.67 (99% CI 0.21 to 207.87); for the 600 mg group, OR 0.06 (99% CI 0.00 to 4.00); and for the 800 mg group, OR 21.86 (99% CI 0.34 to 1419.86). Similarly, there was no statistical difference observed in the occurrence of any particular adverse event or of serious adverse events (160).

2. Hospitalisation:

No study reported this outcome.

3. Attendance at school or work:

No study reported this outcome.

4. Extra courses of antibiotics:

a. Time to next course of antibiotics

Not reported by any study

b. Total number of courses of antibiotics:

Lumacaftor- no significant difference between lumacaftor and placebo in the number of exacerbations or extra courses of antibiotics needed (161, 162).

FDL169- From the published abstract for this Phase 1 study, it is unclear whether exacerbations were physician or protocol defined. A total of three participants across all groups were reported to have had an infective respiratory exacerbation; no participants in the 400 mg group, one participant in the 600 mg group, one participant in the 800 mg and one participant in the placebo group (160).

Other studies did not report this outcome.

5. Sweat chloride (change from baseline) as a measure of *CFTR* function:

Lumacaftor: the two studies examining this intervention provided inconsistent findings. The first study found no significant decrease in sweat chloride in once daily 25 mg, 50 mg, 100 mg and 200 mg at 7 days. At day 28, there was a statistically significant decrease in sweat chloride in the 100 mg and 200 mg once daily of -6.13mmol/L (95% CI -12.25 to -0.01) and -8.21 mmol/L (95% CI -14.30 to - 2.12), respectively (162). The second study found no

statistically significant difference between lumacaftor and placebo in change in sweat chloride in its test dose of 200 mg at day 21 (161).

Cavosonstat- No significant difference was found versus placebo in change in sweat chloride (164).

CPX- No significant difference was found versus placebo in change in sweat chloride (165).

4BPA- Both the pilot study and phase 2 found no significant difference in sweat chloride versus placebo (166, 167).

FDL169- This study reported the absolute change in sweat chloride (mmol/L) at 28 days. There was no difference between the 400 mg group and placebo, MD 2.47 (95% CI -4.47 to 9.41) or between the 800 mg group and placebo, MD 3.48 (95% CI -3.35 to 10.31), but there was a greater drop in sweat chloride in the placebo group than the 600 mg group, MD 8.07 (95% CI 0.98 to 15.16) (160).

6. **Radiological measures of lung disease:**

Not reported by any study.

7. **Acquisition of respiratory pathogens:**

The only pathogen stated was *P. aeruginosa.* One study (phase 2 4BPA) stated this pathogen as an outcome which they will report upon, however no results for this were included (167).

8. **Eradication of respiratory pathogens**

Not reported by any study.

9. **Nutrition & growth**

No parameter for this outcome (e.g. weight, BMI) was reported by any study.

4.3.4.2 Dual combination therapy (adapted from first version of review)

No new dual combination trials were identified by the latest search. Therefore, this provides a summary of dual combination results from the previous edition of this review.

Primary outcomes

1. **Survival:**

No deaths were reported by any of the studies.

2. **Quality of Life:**

a. Total QoL score:

Lumacaftor-ivacaftor:

TRAFFIC & TRANSPORT reported total EuroQol 5 dimension- 3 Level Index at 6 months. No statistical difference vs. placebo was observed. No other studies reported total quality of life score (170).

b. QoL sub-domains:

Lumacaftor-ivacaftor:

A statistically significant improvement versus placebo in CFQ-R respiratory domain was reported at 28 days in the lumacaftor-ivacaftor 600 mg once daily-250 mg twice daily and 400 mg twice daily-250 mg twice daily (mean difference (MD) 3.32 (95% CI: 1.13 to 5.51) and 4.13 (95% CI: 1.94 to 6.31), respectively). At 6 months the statistically significant improvement was maintained in the 600 mg group (MD 3.04 (95% CI 0.76 to 5.32)), but not in the 400 mg group (MD 2.18 (95% CI -0.11 to 4.47)), but when the results for these doses were pooled there was still a statistically significant improvement in CFQ-R at 6 months (170).

At this time point, a statistically significant improvement in the EuroQol 5D-3L visual analogue scale domain was reported in both these dose levels, and when pooled (170).

A study of lumacaftor-ivacaftor in children reported on change CFQ-R respiratory domain at day 15 and weeks 4, 16 and 24. Improvements were seen but were not statistically significant.

Tezacaftor-ivacaftor:

At 4 weeks, a statistically significant improvement in the CFQ-R respiratory domain was seen in one trial (n=510) (MD 5.10 (95% CI 2.99 to 7.21)). This trial also reported a statistically significant improvement versus placebo at 24 weeks (MD 5.10 (95% CI 3.20 to 7.00)) (169). In a second trial (n=18), change in CFQ-R respiratory domain at 4 weeks was reported as 6.81 points (P = 0.2451) (100).

3. Physiological measures of lung function:

a. FEV_1 relative change from baseline:

Lumacaftor-ivacaftor:

TRAFFIC and TRANSPORT did not report relative FEV_1 change at 4 weeks, but did report it at 6 months, when both dose groups had a statistically significant improvement (600 mg OD: MD 5.63 (95% CI 3.80 to 7.47), 400 mg BD: MD 4.77 (95% CI 2.93 to 6.61).

Tezacaftor-ivacaftor:

One trial (n=504) found no significant difference versus ivacaftor alone at 4 weeks in relative change in FEV_1 from baseline (100). Another trial (n=510) found at 24 weeks there was a significant improvement in relative change in FEV_1 from baseline versus placebo (MD 6.80 (95% CI 5.30 to 8.30)) (169).

b. FEV_1 (absolute values)

Lumacaftor-ivacaftor:

Statistically significant improvements were seen in FEV_1 absolute values in TRAFFIC and TRANSPORT at day 28 for both the 600 mg OD and 400 mg BD groups (MD 2.32 (95% CI 1.34 to 3.31) and 2.42 (95% CI 1.43 to 3.40), respectively (170). Another study reported improvements in FEV_1 absolute values that were not statistically significant at day 21 (161).

Tezacaftor-ivacaftor:

Both tezacaftor studies reported a statistically significant improvement in FEV_1 absolute values at 4 weeks (100, 169).

c. FVC

Not reported by any of the dual combination studies.

d. LCI

The paediatric lumacaftor-ivacaftor study also reported a statistically significant decrease versus placebo in lung clearance index 2.5 ($LCI_{2.5}$- the amount of times a person's total lung volume turns over in their lungs in order for the concentration of tracer to reach 2.5% of its starting concentration). The MD was -1.10 (95% CI -1.40 to -0.80) which in this case indicated a desirable change (168).

e. Other measures of lung function

No included trial reported upon outcomes in this category.

Secondary outcomes

1. Adverse events:

Lumacaftor-ivacaftor:

TRAFFIC & TRANSPORT found a statistically significant increase in shortness of breath in the lumacaftor 600 mg OD- ivacaftor 250 mg BD group versus placebo (OR 2.05 (99% CI 1.10 to 3.83)), this significance was also maintained when the 600 mg OD and 400 mg BD results were pooled (OR 1.90 (99% CI 1.08 to 3.35)). They also found cough to be statistically significantly lower in the lumacaftor 400 mg BD- ivacaftor 250 mg OD group versus placebo (OR 0.58 (99% CI 0.39 to 0.88)), significance was also maintained when pooled with the 600 mg OD group (OR 0.65 (99% CI 0.46 to 0.92)) (170).

A statistically significant mean increase in blood pressure over the 120 week study period of the PROGRESS extension to TRAFFIC & TRANSPORT was observed with an increase in systolic blood pressure of 5.1 (SE: 1.5) mm Hg and an increase in diastolic blood pressure of 4.1 (SE: 1.2) mm Hg (n=80) (171). Aside from what is mentioned here, none of the trials found any other statistically significant differences in the occurrence or severity of adverse events across a range of doses of lumacaftor-ivacaftor versus placebo (161, 168, 170, 171).

Tezacaftor-ivacaftor:

No statistically significant difference was found versus placebo or control (ivacaftor alone) in the occurrence or severity of adverse events by either of the included trials for this intervention (100, 169).

2. **Hospitalisation:**

Lumacaftor-ivacaftor:

The lumacaftor 600 mg OD group had a rate of events leading to hospitalisation 39% lower than placebo (0.45 versus 0.27, respectively, P=0.003). The 400 mg BD group had a rate of events leading to hospitalisation of 0.18, this corresponds to a 61% lower rate than placebo (P<0.001) (170).

Tezacaftor-ivacaftor:

One trial reports the occurrence of pulmonary exacerbations which require hospitalisation. This was lower in the intervention group than in the placebo group (0.29 vs. 0.54 events per year, corresponding to a rate ratio of 0.53 (95% CI 0.34 to 0.82) (168).

3. **Attendance at school or work:**

Not reported by any included study.

4. **Extra courses of antibiotics:**

Lumacaftor-ivacaftor:

TRAFFIC & TRANSPORT found both the 600 mg OD and 400 mg BD groups to have a statistically significant increase in the time to first pulmonary exacerbation (hazard ratio: 600 mg OD group: 0.70 (95% CI 0.57 to 0.87), 400 mg BD group: 0.61 (95% CI 0.49 to 0.76). Both doses also led to a statistically significant decrease in the rate of exacerbations when compared to placebo (rate ratio: 600 mg OD group: 0.70 (95% CI 0.57 to 0.87), 400 mg BD group: 0.61 (95% CI 0.49 to 0.76). TRAFFIC & TRANSPORT also led to a statistically significant decrease in the total number of pulmonary exacerbations requiring antibiotics over 48 weeks (odds ratio: 0.66 (99% CI 0.45 to 0.97) and 0.57 (99% CI 0.39 to 0.84), respectively (170). But another study (n=62) found no significant difference between intervention and placebo in the number of exacerbations reported at day 21 (161). The paediatric study also found no statistically significant difference in the number of pulmonary exacerbations (168).

Tezacaftor-ivacaftor:

One trial reported tezacaftor-ivacaftor led to a statistically significantly longer time to first pulmonary exacerbation versus placebo (hazard ratio: 0.64 (95% CI 0.46 to 0.89)) (169).

5. **Sweat chloride (change from baseline) as a measure of CFTR function:**

Lumacaftor-ivacaftor:

One study found that at day 21 (after 14 days of lumacaftor monotherapy followed by 6 days of lumacaftor-ivacaftor combination therapy, there was a statistically significant decrease versus placebo in the concentration of sweat chloride in both the lumacaftor 200 mg OD- ivacaftor 150 mg BD and the lumacaftor 200 mg OD-ivacaftor 250 mg BD groups: MD -5.00 mmol/L (95% CI -11.60 to 1.60) and -10.90 mmol/L (95% CI -17.60 to -4.20), respectively (161). The paediatric trial also found lumacaftor-ivacaftor to have a statistically significantly greater reduction in sweat chloride when compared to placebo at 4 weeks (MD -20.80 mmol/L (95% CI -23.40 to -18.20)) (168).

Tezacaftor-ivacaftor:

2 studies found a statistically significantly greater reduction in sweat chloride concentration versus placebo at 4 weeks. Their pooled MD was -9.24 mmol/L (95% CI -11.12 to -7.35) (100, 169). Of these two studies, one of them carried on to 24 weeks, where it found there to still be a statistically significantly greater decrease in sweat chloride concentration (MD -10.10 mmol/L (95% CI -11.40 to -8.80)) (169).

6. **Radiological measures of lung disease**
7. **Acquisition of respiratory pathogens**
8. **Eradication of respiratory pathogens**

None of outcomes 6,7 or 8 were reported by any included study**.**

9. **Nutrition and growth**

Lumacaftor-ivacaftor:

TRAFFIC & TRANSPORT showed a statistically significantly greater absolute weight gain at 6 months when compared to placebo for both the 600 mg OD and 400 mg BD groups (MD: 0.80 kg (95% CI 0.42 to 1.18) and 0.65 kg (95% CI 0.27 to 1.03), respectively). At 6 months both groups also had a statistically significantly greater absolute gain in BMI (MD: 0.29 (95% CI 0.16 to 0.43) and 0.25 (95% CI 0.12 to 0.39), respectively (170). The paediatric trial did not report weight, despite stating it as an outcome of interest; however, it did report BMI at 6 months by absolute change from baseline BMI and absolute change in BMI-for-age z score. Its reported changes in BMI were not statistically significant (168).

Tezacaftor-ivacaftor:

One of the tezacaftor trials reported on BMI, however it did not find a statistically significant difference between intervention and placebo at either 4 weeks or 24 weeks (169).

Summarising monotherapy & dual combination therapy- adaptations from previous review plus addition of new data.

The correctors which have so far been tested in monotherapy have not shown significant improvements versus placebo in the stated outcomes of interest in the trials and the Cochrane systematic review. When used in dual combination with a potentiator, small but statistically significant improvements in several important outcomes were seen, but notable side effects of transient increased shortness of breath and long-term blood pressure increases were also found to be statistically significant.

4.3.4.3 Triple combination therapy (new data)

Included studies

The newly included triple therapy studies are summarised in the below table.

Trial	Intervention	Control	Target group	Number of patients	Duration
Davies 2018a	VX-659-tezacaftor-ivacaftor or VX-659-tezacaftor-VX-561	Placebo-tezacaftor-ivacaftor or triple placebo	Adults with CF with either F508del/minimal function or F508del/F508del genotypes	12 (9 to intervention, 3 to control)	2 weeks
Davies 2018b	VX-659-tezacaftor-ivacaftor	Triple placebo	Adults with CF with F508del/minimal function genotypes.	117 (90 to intervention, 27 to control)	4 weeks
Keating 2018	VX-445-tezacaftor-ivacaftor	Placebo-tezacaftor-ivacaftor (for F508del/F508del or triple placebo for F508del/minimal function.	Adults with CF with F508del/minimal function of F508del/F508del genotypes.	123 (96 to intervention 27 to control)	4 weeks

Table 6: *Table summarising the methodologies of the newly included triple therapy studies.*

Participants

Three of the new studies (Davies (a) & (b), Keating) recruited people with CF who had one copy of the F508del *CFTR* variant and one copy of a minimal function (MF) variant, which means it is not responsive to ivacaftor alone. Davies b and Keating also recruited another group of participants with two copies of F508del (151, 152). All of the new studies recruited adults only.

Interventions

The three new triple combination studies examined either VX-659-tezacaftor-ivacaftor versus placebo (Davies a & Davies b) or active control of tezacaftor-ivacaftor (Davies b) or VX-445-tezacaftor-ivacaftor versus placebo of active control of tezacaftor-ivacaftor (Keating).

Outcomes

All of the new studies reported lung function by means of FEV_1. They also all reported quality of life using the CFQ-R respiratory domain, as well as adverse effects and change in

sweat chloride concentration. Davies (a & b) and Keating reported on pulmonary exacerbations. None of the studies reported specifically on hospitalisation rates (151, 152).

Funding sources

Pharmaceutical companies funded all 3 of these new studies.

Correctors plus potentiators (triple combination therapy)

A single two-week Phase 1 study (n = 12) compared VX-659 120 mg and ivacaftor 150 mg every 12 hours plus tezacaftor 100 mg once daily versus equivalent placebo in participants whose genotype was F508del/MF variant (Davies 2018a) (152).

One four-week Phase 2 study compared three doses of VX-659 with tezacaftor and ivacaftor versus a single placebo group (n = 10) in participants with an F508del/MF genotype (n = 53) as follows:

VX-659 80 mg and tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 11);
VX-659 240 mg and tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 20);
VX-659 400 mg and tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 22).

These groups taking one of the doses had a four-day washout period taking tezacaftor-ivacaftor only (same doses). This Phase 2 study also included a group to test once daily VX-659 400 mg plus tezacaftor 100 mg plus VX-561 (deuterated ivacaftor) 150 mg versus placebo in another group of participants with an F508del/MF variant genotype (n = 25) for four weeks. In another arm of the study, 29 participants who were homozygous for F508del were randomised to either VX-659 400 mg plus tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 18) or to placebo plus tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (this dual therapy combination is currently considered the standard of care for people with this genotype) (n = 11). This cohort (n = 29) had a four-week run-in period taking the same dose of tezacaftor-ivacaftor only before starting the triple therapy combination for another four weeks. Once the intervention period was over, these participants had a further four-week washout period where they reverted to the same dose of tezacaftor-ivacaftor as a dual combination (Davies 2018b) (152).

A different Phase 2 study evaluated three different doses of VX-445 versus placebo (n = 12) in participants with F508del/MF for a four week period, followed by a washout period of tezacaftor plus ivacaftor or dual placebo lasting one week. The intervention doses were:

VX-445 50 mg and tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 10); VX-445 100 mg and tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n = 14); and VX-445 200 mg and tezacaftor 200 mg once daily plus ivacaftor 150 mg twice daily (n = 21). This same trial also compared once daily VX-445 200 mg plus tezacaftor 100 mg plus VX-561 150 mg to triple placebo in another group of participants with a F508del/MF genotype (n = 29); these participants did not have a run-in period or a washout period. In the same study, another group of participants homozygous for F508del (n = 28) had a four-week run-in of once daily tezacaftor 100 mg plus ivacaftor 150 mg, followed by the intervention period of once daily VX-445 200 mg or equivalent placebo while continuing the same doses of tezacaftor and ivacaftor; this was then followed with a washout period where all participants took just tezacaftor and ivacaftor at the previous doses for a further four weeks (Keating 2018) (151).

Primary outcomes

1. Survival:

   No deaths reported by any of the triple therapy trials.

2. QoL:

   a. Total QoL score: Not reported by any of these studies

   b. QoL sub-domains:

      The two phase 2 studies reported on CFQ-R respiratory domain:

      <u>VX-659 plus tezacaftor plus ivacaftor</u>

      Participants with F508del/MF:

      One study (n = 117) reported on the absolute change in the CFQ-R respiratory domain following four weeks of treatment (Davies 2018b). For the 80 mg dose (n = 11), the change in score was statistically significant in favour of the intervention versus placebo, MD 10.00 (95% CI 0.29 to 19.71). No significant difference was observed for the 240 mg group (n = 20), MD 4.00 (95% CI -4.70 to 12.70) or the 400 mg group (n = 22), MD 7.90 (95% CI -0.58 to 16.38) (152).

      Participants with F508del/F508del:

One study reported a statistically significant improvement in the respiratory domain of CFQ-R at the 400 mg dose level of VX-659 versus active control of placebo-tezacaftor-ivacaftor (n = 10) (Davies 2018b), MD 18.10 (95% CI 10.85 to 25.35) (152).

VX-659 plus tezacaftor plus VX-561

One study tested this regimen in another group of participants with F508del/MF (Davies 2018b). The only dose of VX-659 tested in this group was 400 mg (n = 19). A statistically significant improvement versus placebo in the respiratory domain was observed, MD: 20.3 (95% CI 7.1 to 33.6) (152).

VX-445 plus tezacaftor plus ivacaftor

Participants with F508del/MF:

In one study (Keating 2018), VX-445 led to a statistically significant improvement against placebo in the respiratory domain of CFQ-R for the 50 mg dose (n = 10), MD 17.20 (95% CI 4.44 to 29.96), the 100 mg dose (n = 22), MD 14.50 (95% CI 3.72 to 25.28) and for the 200 mg dose (n = 21), MD 21.30 (95% CI 10.52 to 32.08) (151).

Participants with F508del/F508del:

The study conducted by Keating reported a statistically significant improvement in the CFQ-R respiratory domain for the 200 mg group (n = 21) versus the placebo-tezacaftor-ivacaftor group (n = 7), MD 19.30 (95% CI 8.34 to 30.26) (151).

VX-445 plus tezacaftor plus VX-561

This regimen was tested in another group of F508del/MF participants, but the only dose tested was VX-445 200 mg (n = 21). A statistically significant improvement in the respiratory domain of CFQ-R at 4 weeks was observed when compared to placebo, MD 12.80 (95% CI 0.93 to 24.67) (151).

No triple therapy trial reported on quality of life beyond the 4-week study period of the trials.

3. Physiological measures of lung function:

a. FEV_1 (relative change from baseline)

i. Immediate term (up to and including one month)

Two trials reported on this outcome at the four week time point (Davies 2018b; Keating 2018).

VX-659 plus tezacaftor plus ivacaftor

Participants with F508del/MF:

One study reported a statistically significant improvement favouring the test intervention against placebo at the 80 mg dose level (n = 11), MD 18.36 (95% CI 3.63 to 33.09), the 240 mg dose level (n = 20), MD 20.17 (95% CI 8.73 to 31.61) and also the 400 mg dose level (n = 22), MD 23.85 (95% CI 14.52 to 33.18) (152).

Participants with F508del/F508del:

One study reported a statistically significant difference in the relative change in FEV_1 % predicted in the 400 mg group (n = 18) when compared with placebo-tezacaftor-ivacaftor (n = 11), MD 15.99 (95% CI 8.61 to 23.37) (152).

VX-659 plus tezacaftor plus VX-561

Participants with F508del/MF:

This regimen was tested with a single dose level of VX-659 400 mg in this group of participants. It led to a statistically significant improvement in the relative change from baseline in FEV_1 against placebo (n = 6), MD 33.05 (95% CI 22.05 to 44.05) (152).

VX-445 plus tezacaftor plus ivacaftor

Participants with F508del/MF:

The test intervention led to statistically significant improvements against placebo at each included dose level of VX-445: at 50 mg (n = 10), MD 19.0 (95% CI 7.08 to 30.92); 100 mg (n = 22), MD 13.5 (95% CI 3.28 to 23.72); and 200 mg (n = 21), MD 25.90 (95% CI 15.57 to 36.23) (151).

Participants with F508del/F508del:

In this group of people with CF with this genotype, one study reported a statistically significant improvement in relative change from baseline in FEV_1 percent predicted in favour of the test intervention (200 mg dose) when compared against placebo-tezacaftor-ivacaftor (n = 7), MD 17.80 (95% CI 6.66 to 28.94) (151).

VX-445 plus tezacaftor plus VX-561

Participants with F508del/MF:

The only dose level of VX-445 tested in this group was 200 mg, the study reports a statistically significant improvement for the test intervention group against placebo (n = 8), MD 18.30 (95% CI 7.64 to 28.96) (151).

ii. Short term (over one month and up to and including six months)

None of the triple therapy trials reported for time points longer than one month.

b. FEV_1 absolute values

All three triple combination studies reported on absolute FEV_1 values; two studies reported the absolute change in L (Davies 2018b; Keating 2018) and one study reported the absolute change in % predicted (Davies 2018a).

i. Immediate term (up to and including one month):

<u>VX-659 plus tezacaftor plus ivacaftor</u>

Participants with F508del/MF:

A statistically significant improvement was seen in the absolute change in FEV_1 (L) with the intervention regimen versus placebo for the 80 mg dose (n = 11), MD 0.37 L (95% CI 0.15 to 0.59), for the 240 mg (n = 20), MD 0.42 L (95% CI 0.20 to 0.64), and for the 400 mg dose (n = 22) MD 0.52 L (95% CI 0.34 to 0.70) (152). The Davies (a) study reporting the absolute change in FEV_1 % predicted only looked at a treatment regimen using VX-659 120 mg twice per day in participants with the genotype F508del/MF and found that the intervention significantly improved FEV_1 % predicted compared to placebo (n=3), MD 10.00 (95% C: 3.04 to 16.96) (152).

Participants with F508del/F508del:

One study reported the absolute change in FEV_1 (L) (Davies 2018b). Only a dose of VX-659 400 mg was tested in this population and the study found a statistically significant improvement in favour of the intervention compared to the control group (n = 11), MD 0.35 L (95% CI 0.19 to 0.51) (152).

<u>VX-659 plus tezacaftor plus VX-561</u>

In this group of participants, all of whom had a F508del/MF genotype, only a dose of VX-659 400 mg was tested and showed a statistically significant improvement in favour of the intervention compared to placebo (n = 6), MD 0.68 L (95% CI 0.45 to 0.91) (152).

VX-445 plus tezacaftor plus ivacaftor

Participants with F508del/MF:

This triple therapy combination led to statistically significant improvements at all doses of the test intervention compared to placebo: 50 mg (n = 10) MD 0.46 L (95% CI0.19, 0.73); 100 mg group (n = 22), MD 0.38 L (95% CI 0.20 to 0.56); and 200 mg group (n = 21), MD 0.57 L (95% CI 0.36 to 0.78) (151).

Participants with F508del/F508del:

Only VX-445 200 mg was tested in this group (n = 21). Results showed a statistically significant improvement in absolute change in FEV_1 (Litres) versus placebo-tezacaftor-ivacaftor (n = 7), MD 0.46 L (95% CI 0.26 to 0.66) (151).

VX-445 plus tezacaftor plus VX-561

Participants with F508del/MF:

Only a dose of VX-445 200 mg was tested in this group and results showed a statistically significant improvement in the absolute change in FEV_1 (L) versus placebo (n = 8), MD 0.44 L (95% CI 0.25 to 0.63) (151).

c. FVC (absolute values and change from baseline)

Not reported by any of the included triple therapy studies.

d. LCI

Not reported by any of the included triple therapy studies.

Secondary outcomes

1. Adverse events

   Adverse events were reported by all of the studies examining triple combination therapies. All three of the studies reported adverse events as according to mild, moderate or severe; they also recorded the "most common adverse events" which they defined as occurring in at least 5% participants. We have set CIs for adverse events at 99%, as per "measure of treatment effect" in this review's methodology.

   <u>VX-659 plus tezacaftor plus ivacaftor versus placebo</u>

   There was no significant difference in the number of participants experiencing at least one adverse event between the test intervention and placebo at any dose or for any genotype. For each VX-659 dose level, the ORs and their corresponding 99% CIs were as follows: 80 mg (n = 11), OR 1.11 (99% CI 0.02 to 51.19); 120 mg twice daily (n = 9), OR 31.67 (99% CI 0.32 to 3111.29); 240 mg (n = 20), OR 0.33 (99% CI 0.02 to 6.85); 400 mg (for participants with F508del/MF) (n= 22), OR 0.38 (99% CI 0.02 to 7.70); 400 mg (for participants with F508del/F508del) (n = 18), OR 1.25 (99% CI 0.05 to 34.62) All doses are once daily except for 120 mg, which was taken twice daily in the Phase 1 study (152).

   <u>VX-659 plus tezacaftor plus VX-561 versus placebo</u>

   For this comparison, there was no significant difference in adverse events between the test intervention and placebo (n = 6), OR 0.95 (99% CI 0.01 to 74.78) (152).

   <u>VX-445 plus tezacaftor plus ivacaftor versus placebo</u>

   No statistically significant differences in the number of adverse events were observed between the intervention and placebo groups. In the 50 mg cohort, every participant in both the intervention and placebo groups had an adverse event, therefore an OR was not estimable. For every other dose, their corresponding ORs and CIs are: 100 mg (n = 22), OR 0.57 (99% CI 0.01 to 42.46); 200 mg (for participants with F508del/MF) (n = 21), OR 0.21 (99% CI 0.00 to 11.62); and for 200 mg (for participants with F508del/F508del), (n = 21), OR 3.80 (99% CI: 0.21 to 67.89) (151).

VX-445 plus tezacaftor plus VX-561 versus placebo

No statistically significant difference in the number of adverse events were observed between the intervention (n= 21) and placebo (n = 8) groups, OR 1.36 (99% CI 0.05 to 38.84) (151).

a. Mild (therapy does not need to be discontinued)

We could not accurately record the number of mild adverse events occurring in any of the triple therapy studies since they record the number of participants experiencing at least one adverse event, by the maximum severity, meaning that a participant may have had numerous 'mild' adverse events and a single moderate or severe event, but we would only be aware of the single most severe event (151, 152).

b. Moderate (therapy is discontinued, and the adverse effect ceases)

Our definition of a moderate adverse effect differed to that used in the studies, however the studies also reported the number of adverse events which led to discontinuation of therapy. We therefore used this number to record the number of moderate adverse events according to our definition.

VX-659 plus tezacaftor plus ivacaftor

No participants in either the intervention or placebo groups were recorded as having a moderate adverse event in any of the dose groups (VX-659 80 mg, VX-659 120 mg 2 x daily group, VX-659 400 mg for participants with F508del/MF and with F508del/F508del), meaning an OR was not calculable.

For the VX-659 240 mg group, there was no statistically significant difference in the number of moderate adverse events between the intervention (n = 20) and placebo groups (n = 10), OR 1.62 (99% CI 0.02 to 121.50) (152).

VX-659 plus tezacaftor plus VX-561

No statistically significant difference was observed in the number of moderate adverse events between the intervention (n = 19) and placebo groups (n = 6) in this treatment regimen group, OR 1.86 (99% CI 0.03 to 119.25) (152).

VX-445 plus tezacaftor plus ivacaftor

No participants in either the In the VX-445 50 mg or the VX-445 100 mg groups or the placebo groups were recorded as having a moderate adverse event, meaning an OR was not calculable for the groups taking this dose (151).

There were no statistically significant differences in the number of moderate adverse events experienced by the intervention and placebo groups across all doses and genotypes: VX-445 200 mg (participants with F508del/MF) (n = 21), OR 0.31 (99% CI 0.04 to 2.28); and VX-445 200 mg (participants with F508del/F508del) (n = 21) OR 1.54 (99% CI 0.1 to 17.8) (151).

VX-445 plus tezacaftor plus VX-561

No participants in either the intervention or placebo groups experienced a moderate adverse effect, meaning an OR was not calculable for this group (151).

c. Severe (life-threatening or debilitating, or which persists even after stopping treatment)

Our definition of severe adverse events was equivalent to the studies' definition of a serious adverse event; therefore we counted the number of participants reporting serious adverse events.

VX-659 plus tezacaftor plus ivacaftor

Severe adverse events occurred at every dose level and for both F508del/F508del and F508del/MF participants. The severe events occurred in the intervention and placebo groups and there was no statistically significant difference between intervention and placebo. Respective ORs and 99% CIs for each group were: VX-659 80 mg (n = 11), OR 0.23 (99% CI 0.01 to 5.92); VX-659 120 mg twice daily (n = 9), OR 2.33 (99% CI 0.03 to 176.29); VX-659 240 mg (n = 20), OR 0.58 (99% CI 0.06 to 5.75); VX-659 400 mg (participants with F508del/MF) (n = 22), OR 0.11 (99% CI 0.00 to 2.67); VX-659 400 mg (participants with F508del/F508del) (n = 18), OR 0.26 (99% CI 0.01 to 7.39) (152).

VX-659 plus tezacaftor plus VX-561

No statistical difference was found between the intervention (n=19) and placebo (n=6) groups for the number of severe adverse effects for this group OR: 0.12 (99% CI 0.01 to 2.04) (152).

VX-445 plus tezacaftor plus ivacaftor

No statistically significant differences were observed between the intervention and placebo groups, across all doses and genotypes. Results for each of the dose and genotype groups are as follows: VX-445 50 mg (n = 10), OR 0.56 (99% CI 0.02 to 16.15); VX-445 100 mg (n = 22), OR 0.50 (99% CI 0.03 to 7.92); VX-445 200 mg (participants with F508del/MF) (n = 21), OR 0.10 (99% CI 0.00 to 5.93); VX-445 200 mg (participants with F508del/F508del) (n = 21), OR 0.10 (99% CI 0.00 to 7.90) (151).

VX-445 plus tezacaftor plus VX-561

None of the 21 participants in the intervention group and one out of eight participants in the placebo group experienced a severe adverse event. There was no statistically significant difference observed between the groups (total n = 29), OR 0.12 (99% CI 0.00 to 8.97) (151).

2. Hospitalisation

   Not reported by any of the included triple therapy studies.

3. Attendance at work or school

   Not reported by any of the included triple therapy studies.

4. Extra courses of antibiotics

   a. Time-to the next course of antibiotics

      Not reported by any of the included triple therapy studies.

b. Total number of courses of antibiotics

Like previously, under this outcome, we will report on the occurrence of infective pulmonary exacerbations.

VX-659 plus tezacaftor plus ivacaftor

Davies' phase 1 study found that in the 120 mg twice daily group, two out of nine participants in the test group and none of the three participants in the placebo group had an infective pulmonary exacerbation, OR 2.33 (95% CI 0.03 to 176.29) (152).

Davies' phase 2 study found that in the 80 mg group, three out of 11 participants in the intervention group and two out of 10 participants in the placebo group had an exacerbation, OR 1.50 (95% CI 0.10 to 21.90); in the 240 mg once daily group, three out of 20 participants in the intervention group and two out of 10 in the placebo group had an exacerbation, OR 0.71 (95% CI 0.05 to 9.48); in the 400 mg F508del/MF group, four out of 22 participants in the intervention group and two out of 10 in the placebo group had an exacerbation, OR 0.89 (95% CI 0.07 to 10.67); in the 400 mg F508del/F508del group five out of 18 participants in the intervention group and three out of 11 in the placebo group had an exacerbation, OR 1.03 (95% CI 0.11 to 9.34) (152).

VX-659 plus tezacaftor plus VX-561

Davies found that two out of 19 participants in the intervention group and three out of six participants in the placebo group had an exacerbation, OR 0.12 (95% CI 0.01 to 2.04) (152).

VX-445 plus tezacaftor plus ivacaftor

Keating found that in the 50 mg group, three out of 10 participants in the intervention group and four out of 12 participants in the placebo group had an infective pulmonary exacerbation, OR 0.86 (95% CI 0.08 to 9.23). In the 100 mg group five out of 22 participants in the intervention group and three out of 12 participants on placebo had an exacerbation, OR 0.59 (95% CI 0.08 to 4.57). In the 200 mg F508del/MF group, two out of 21 on active treatment regimen and four out of 12 on placebo had an exacerbation, OR 0.21 (95% CI 0.02 to 2.52).

In the 200 mg F508del/F508del group, five out of 21 and one out of seven participants in the intervention and placebo groups, respectively, had an exacerbation, OR 1.88 (95% CI 0.09 to 40.77). It was not clear whether the exacerbations were protocol-defined or physician-defined (151).

VX-445 plus tezacaftor plus VX-561

Keating found that in this group, three out of 21 of those on the active regimen and four out of eight participants on placebo had an infective respiratory exacerbation during the study, OR 0.17 (95% CI 0.01 to 1.89) (151).

5. Sweat chloride (change from baseline) as a measure of *CFTR* function

VX-659 plus tezacaftor plus ivacaftor

One phase 1 study found the 120 mg twice-daily active intervention (n = 9) to reduce sweat chloride by 41.6 mmol/L and placebo (n = 3) to reduce sweat chloride by 11.0 mmol/L, MD -30.60 mmol/L (95% CI -46.38 to -14.82) (152).

A phase 2 study found that all active intervention groups showed a significant difference in the change in sweat chloride compared to placebo. The placebo group (n = 10) experienced an increase in sweat chloride by 2.9 mmol/L, whereas the 80 mg intervention group (n = 11) reduced sweat chloride by 45.70 mmol/L, MD -48.60 mmol/L (95% CI -60.94 to -36.26); the 240 mg intervention group (n = 20) reduced sweat chloride by 43.8 mmol/L, MD: -46.70 mmol/L (95% CI -57.91 to -35.49); the 400 mg F508del/MF intervention group (n = 22) reduced sweat chloride by 51.4 mmol/L, MD -54.30 mmol/L (95% CI -65.28 to -43.32); and the 400 mg F508del/F508del group (n = 18) had a sweat chloride reduction of 42.2 mmol/L, MD -45.20 mmol/L (95% CI -52.18 to -38.22) (152).

VX-659 plus ivacaftor plus VX-561

In this group, Davies found placebo (n = 6) to decrease sweat chloride by 1.3 mmol/L, and the intervention group (n = 19) showed a reduction of 38.1 mmol/L, MD -36.80 mmol/L (95% CI -48.74 to -24.86) (152).

VX-445 plus tezacaftor plus ivacaftor

The Keating study found that all active intervention groups in this comparison showed a significant difference in the change in sweat chloride compared to placebo. The placebo group for the ascending dose F508del/MF groups (n = 12) showed a decrease in sweat chloride of 2.2 mmol/L and the 50 mg group (n = 10) showed a decrease of 38.2 mmol/L, MD -36.00 mmol/L (95% CI -47.23 to -24.77); the 100 mg group (n = 22) showed a decrease of 33.2 mmol/L, MD -31.00 mmol/L (95% CI -40.41 to -21.59); the 200 mg F508del/MF group (n = 21) showed a decrease of 39.1 mmol/L, MD -36.90 mmol/L (95% CI -46.43 to -27.37); and the 200 mg F508del/F508del group (n = 21) showed a decrease of 39.6 mmol/L, MD -40.40 mmol/L (95% CI -51.46 to -29.34) (151).

VX-445 plus tezacaftor plus VX-561

Keating found that the placebo group (n = 8) for this group showed an increase of 1.0 mmol/L and the intervention group (n = 21) showed a decrease of 33.6 mmol/L, MD -34.60 mmol/L (95% CI -45.15 to -24.05) (151).

6. Radiological measures of lung disease

7. Acquisition of respiratory pathogens

8. Eradication of respiratory pathogens

9. Nutrition and growth

Outcomes 6, 7, 8 & 9 were not reported by any of the included triple therapy studies.

Pooled efficacy data for triple therapy combinations:

We pooled efficacy data for the varying doses of VX-659 and VX-445, along with data for their combinations with VX-561 (which was considered a similar enough intervention to normal ivacaftor to be included in this meta-analysis, were combined together to examine the overall efficacy of triple therapy combination options. Only data examining triple therapy options in people with CF with the F508del/MF genotypes were included, as they were who the majority of data was collected on and we did not want to introduce genotype as a confounder by including those with F508del/F508del genotypes. This pooled data included adults only, as no children were included as part of the enrolled study population.

We did not pool adverse event data due to the complexity of their measurement and reporting and decided that a narrative description of these results in the individual sections above would provide a better illustration of adverse event data.

Quality of life

Overall, triple therapy (n = 146) significantly improved the CFQ-R respiratory domain score compared to placebo (n = 80), MD 12.03 (95% CI 8.36 to 15.71). Improvements were statistically significant across all combinations and dose levels except for the VX-659 240 mg and 400 mg- tezacaftor- ivacaftor groups (151, 152).

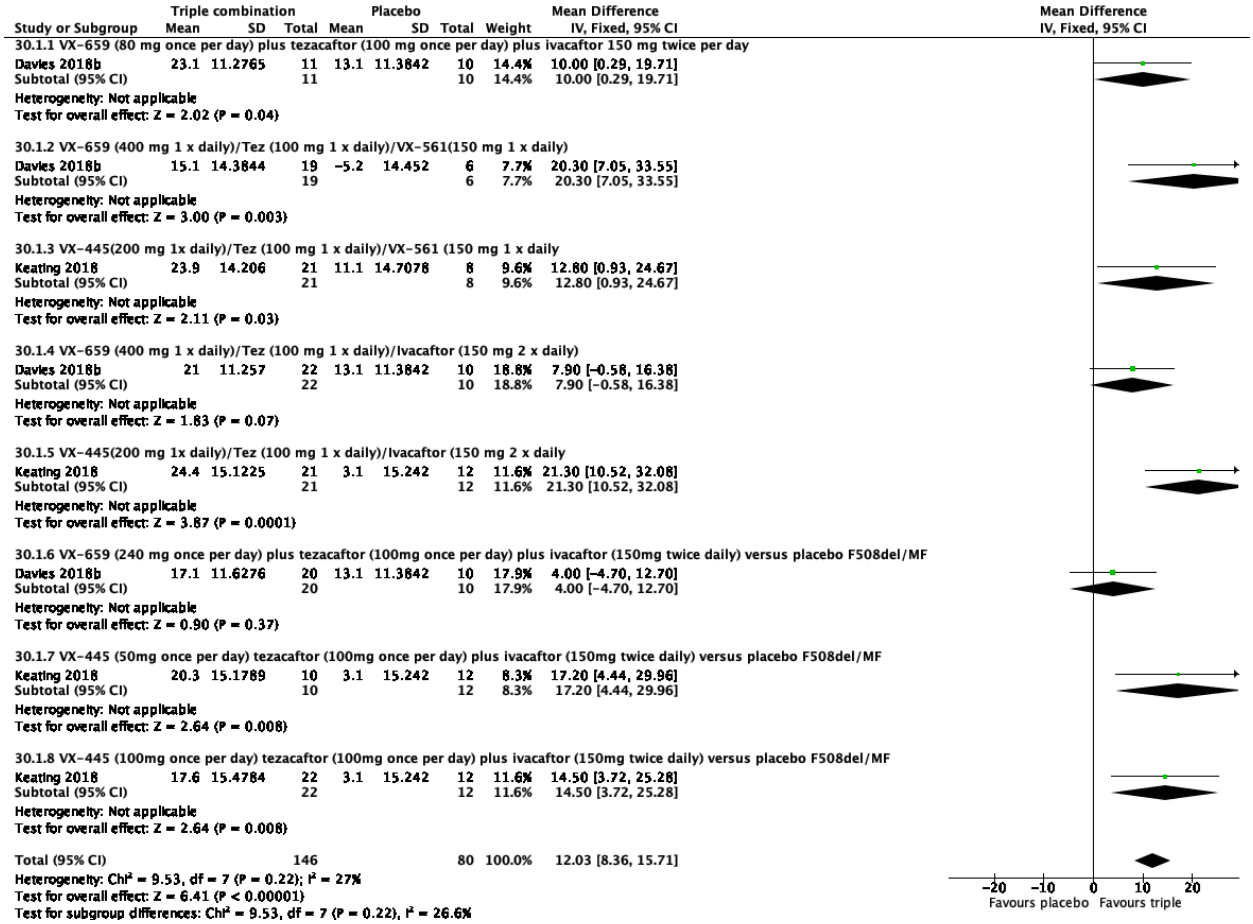

***Figure 6**: Forest plot showing change from baseline in CFQ-R respiratory domain for all dose combinations in participants with F508del/MF genotypes, plus overall pooled result from these data.*

FEV_1 % predicted relative change from baseline

Overall, triple therapy combinations (n = 146) were found to have a statistically significantly improvement in the relative change from baseline in percent predicted FEV_1 versus placebo (n = 80), MD 22.78% (95% CI 18.92 to 26.63). Improvements were statistically significant for all included combinations and dose levels (151, 152).

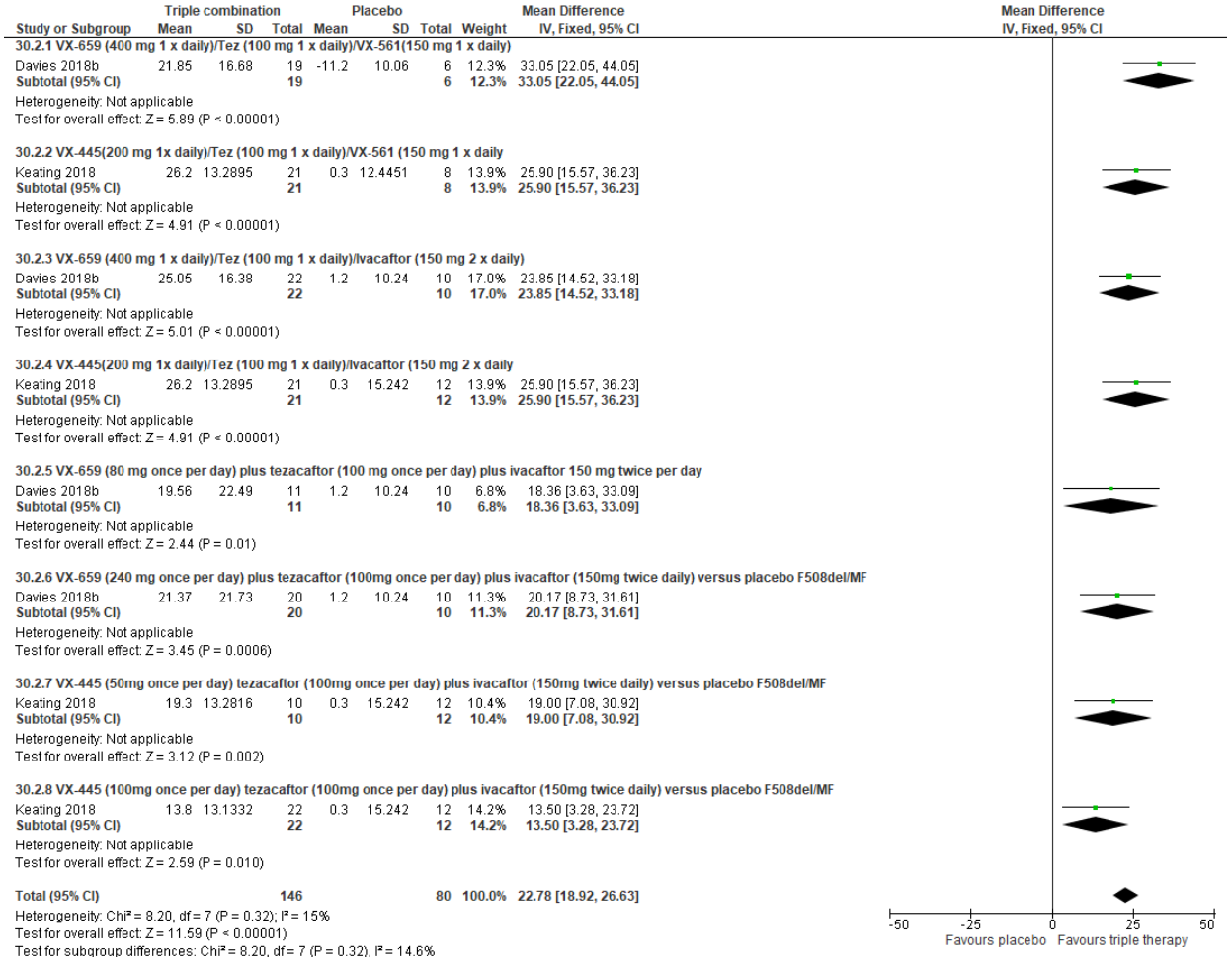

***Figure 7**: Forest plot showing relative change in percent predicted FEV_1 for all dose combinations in participants with F508del/MF genotypes, plus overall pooled result from these data.*

FEV_1 absolute change from baseline

Overall, triple therapy (n = 146) was found to have a statistically significant improvement in absolute change in FEV_1 versus placebo (n = 80), MD: 0.47 L (95% CI 0.40 to 0.55). Improvements were statistically significant for all included combinations and dose levels (151, 152).

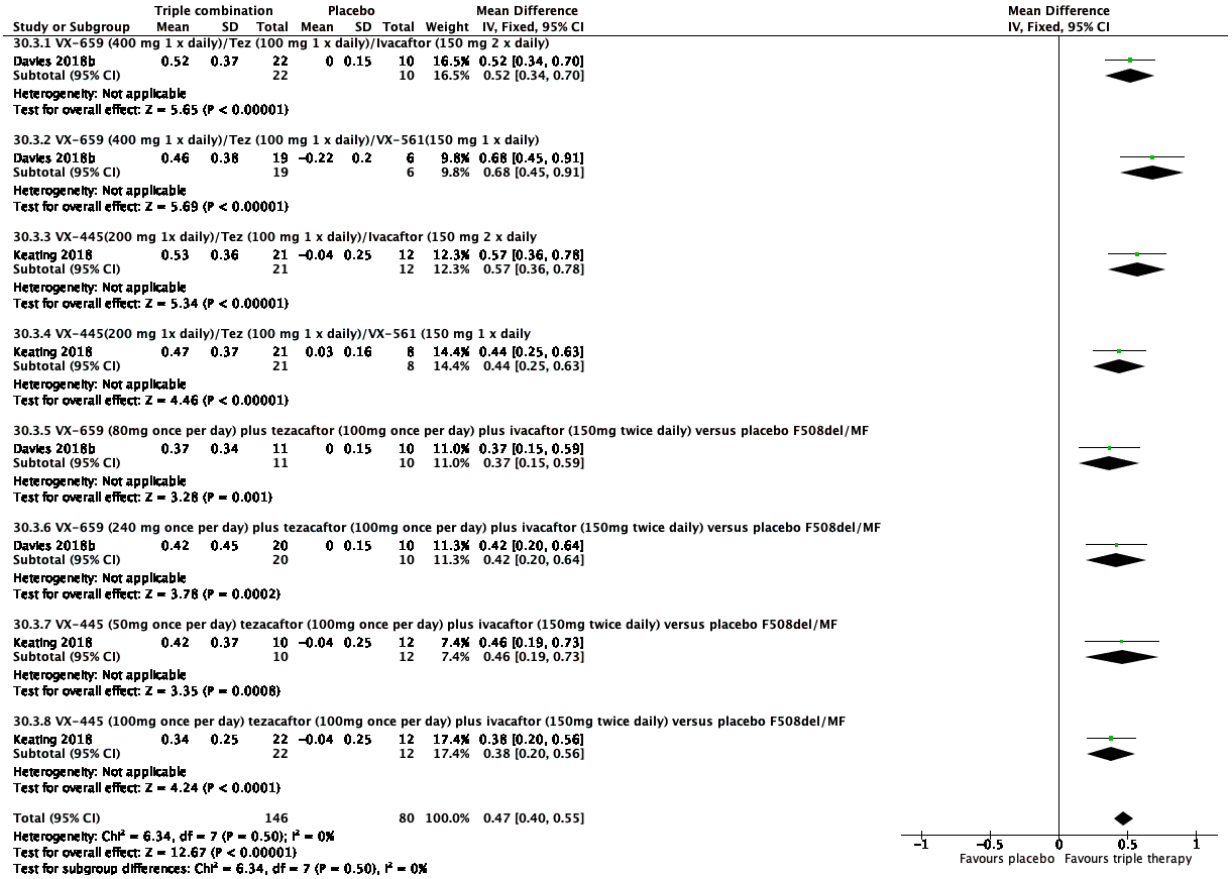

***Figure 8**: Forest plot showing absolute change in FEV_1 for all dose combinations in participants with F508del/MF genotypes, plus overall pooled result from these data.*

Sweat chloride absolute change from baseline

Overall, triple therapy (n = 146) was found to significantly improve the absolute change in sweat chloride from baseline versus placebo (n = 80), MD -39.34 mmol/L (95% CI -43.04 to -35.65). Improvements were statistically significant for all included combinations and dose levels (151, 152).

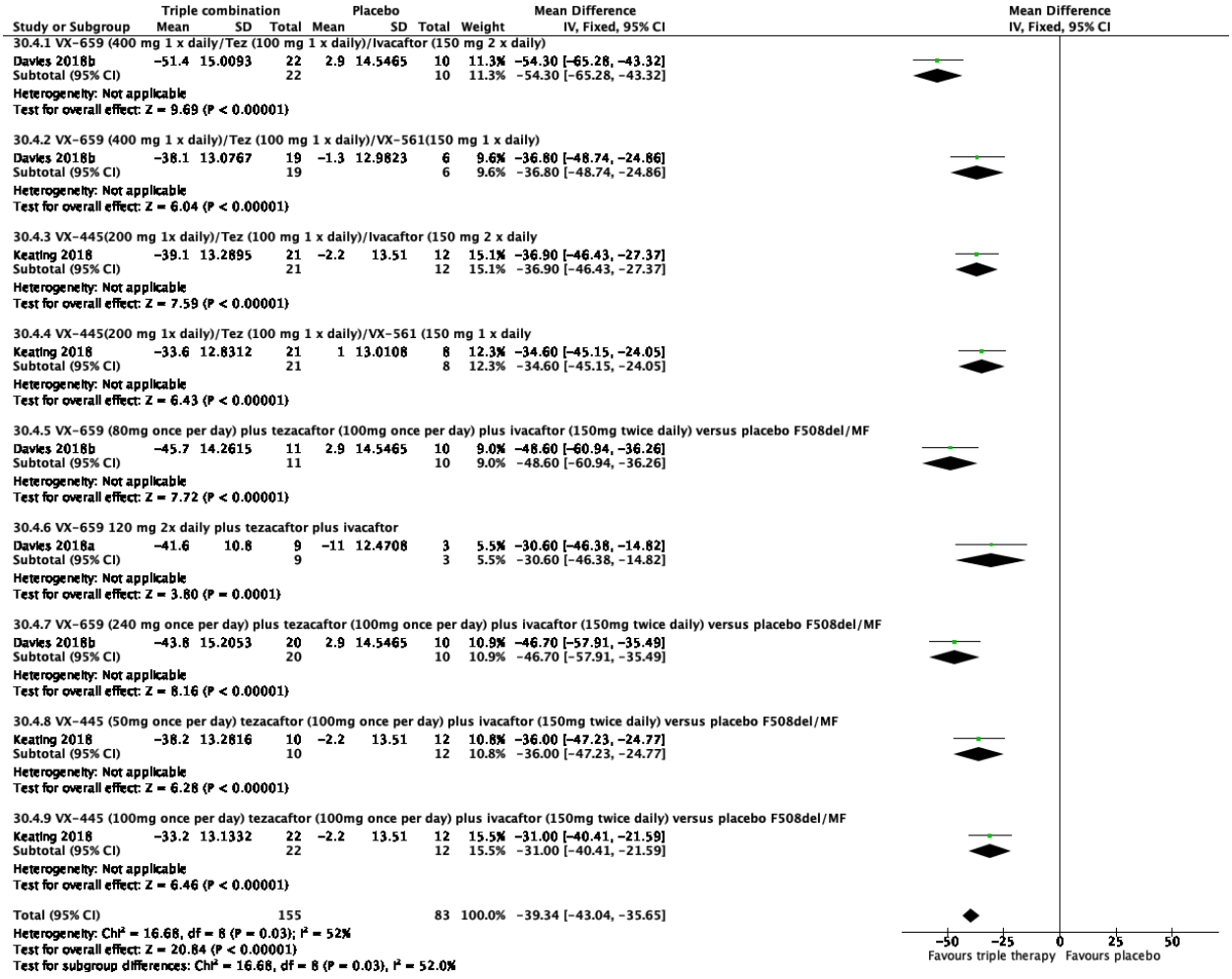

Figure 9*: Forest plot showing change from baseline in sweat chloride for all dose combinations in participants with F508del/MF genotypes, plus overall pooled result from these data.*

We note the I^2 statistic is noticeably larger for this forest plot when compared to the others, despite the graph appearing to be less heterogeneous than others. Following discussion with the team statistician, it is thought that this I^2 statistic value is due to the differences in the magnitude of the changes in sweat chloride for each regimen & dose. It should also be noted that as a result of differing magnitude of changes, the x axes on each forest plot differ in scale. This can make heterogeneity more difficult to compare between the forest plots of the different measures of outcomes.

4.4 Discussion for Cochrane systematic review

F508del, a class II variant is prevalent, especially in those who descend from Northern European ancestry. 80-90% of people with CF have at least one copy of F508del (13). A therapy which effectively corrects the folding defect of class II variants could have a significant impact on the treatment of many people with CF.

4.4.1 Summary of main results

This latest update identified 4 new studies evaluating correctors in people with CF who have at least one F508del variant. One study examined monotherapy with FDL169 versus placebo (Horsley 2017)(160). Three studies examined triple therapy, one phase one study with VX-659-tezacaftor-ivacaftor versus placebo, one phase 2 study with VX-659-tezacaftor-ivacaftor versus placebo or dual combination control (Davies 2018 a & b)(152); and one phase 2 study of VX-445-tezacaftor-ivacaftor versus placebo or dual combination control (Keating 2018) (151).

4.4.1.1 Monotherapy versus placebo or control

The Horsley study found a statistically significant improvement at the 400 mg dose versus placebo in the absolute change in FEV_1 % predicted, MD 4.68 % predicted (95% CI: 0.12 to, 9.24). Though statistically significant, it is uncertain whether this improvement is clinically significant. No such significant changes in FEV_1 were found at other dose levels.

A statistically significant increase was observed in the change from baseline of sweat chloride for the 600 mg dose of FDL169 versus placebo, MD 8.84 mmol/L (95% CI 1.40 to 16.28). No such significant changes in sweat chloride were observed at other tested doses.

There are no significant concerns in safety at any dose when compared to placebo and one abstract stated that FDL169 will be studied in combination with FDL176, a potentiator (160).

4.4.1.2 Double combination therapy versus placebo or control

No new data for double combination therapies was added as of this update. Evidence shows that it can lead small improvements in measures such as pulmonary function, but the combination of lumacaftor-ivacaftor has been associated with significant adverse events such as transient increases in dyspnoea and raised blood pressure. Tezacaftor-ivacaftor has not been associated with these adverse events.

4.4.1.3 Triple combination therapy versus placebo or control

Both triple therapy combinations led to a statistically significant increase in QoL across multiple doses for people with CF who have one or two F508del gene variants. In two of the doses of VX-659 (240 mg and 400 mg) tested in people with the F508del/MF genotype, there was no significant improvement in QoL (151, 152).

For triple combinations including VX-659, there was a significant improvement in both absolute and relative change in FEV_1 from baseline compared to placebo for people with CF with one or two copies of F508del. For the F508del/MF participants in the 400 mg VX-659 group the relative change from baseline was MD 23.9 (95% CI 14.52 to 33.18) and the absolute change for this group was MD 0.52 L (95% CI 0.34 to 0.70). For the F508del/F508del participants, the relative change in FEV_1 from baseline was 16.0% (95% CI 8.6 to 23.4) and the absolute change was MD 0.35 L (95% CI 0.19 to 0.51) (152).

For the VX-445 combination, similar results were found: for the F508del/F508del participants in the 200mg dose group the relative change from baseline in FEV_1 was MD 17.8% (95% CI 6.7 to 28.9) and the absolute change from baseline was MD 0.46 L (95% CI 0.26 to 0.66); and for the F508del/MF participants taking 200 mg. The relative change in FEV_1 was MD 25.90% (95% CI 15.57 to 36.23) and the absolute change FEV_1 was MD: 0.57 L (95% CI 0.36 to 0.78) (151).

There was no statistically significant difference in the occurrence of adverse events for any combination compared to placebo across both genotype groups (study period of four weeks). There were no unexpected adverse events related to the study drug.

A statistically significant decrease in sweat chloride from baseline was observed across all dose regimens of both the VX-659 and VX-445 combinations compared to placebo for people with one or two copies of the F508del variant, e.g. for F508del/F508del participants in the VX-659 400 mg group, MD -45.20 mmol/L (95% CI -52.18 to -38.22) and for the F508del/MF participants in this treatment group, MD -54.30 mmol/L (95% CI -65.28 to -43.32). Similarly, for the F508del/F508del participants in the VX-445 200 mg group, MD -40.40 mmol/L (95% CI -51.46 to -29.34) and for the F508del/MF participants in this group, MD -36.90 mmol/L (95% CI -46.43 to -27.37) (151, 152).

When data were pooled for triple combination therapies in people with CF with F508del/MF genotypes, it was found that triple combination therapies generally led to a statistically significant improvement in the measures of efficacy included in this review.

Participants with the genotype F508del/F508del were not included in this pooling of data as their different genotypes made them too different to be able to include their response to the triple combination therapies as part of the same pooled analysis. As the trials only tested one dose in those with F508del/F508del genotypes, and also did not test VX-561, there were no multiple groups of these participants to be combined together as part of another pooled analysis for this genotype. These homozygous participants were already on tezacaftor-ivacaftor before this trial as they were receiving the standard of care.

4.4.2 Overall completeness & applicability of evidence

4.4.2.1 Monotherapy versus placebo or control

The data available for the phase 1 FDL169 study (Horsley) were only provided in a poster and conference abstract (160).

4.4.2.2 Dual combination therapy versus placebo or control

No new trials of dual combination therapy were identified by this latest update.

4.4.2.3 Triple combination therapy versus placebo or control

The phase 2 trials of triple combination therapy enrolled people with CF homozygous for F508del (F508del/F508del) and also people with CF with one copy of F508del and one MF variant (F508del/MF). They did not include people under 18 years of age. Data on younger people with CF will be required. The duration of the intervention in each study was 4 weeks, meaning that more long term data on efficacy and safety will also be required (151, 152).

The phase 2 studies tested the triple therapy combination of VX-659 or VX-445 plus tezacaftor 100 mg once daily plus VX-561, a deuterated form of ivacaftor that has a longer half-life in the body than the typical ivacaftor formulation. This means it is taken once daily at the same dose (150 mg), rather than the typical 150 mg twice per day with standard ivacaftor. This combination was only tested in a group of participants with the F508del/MF heterozygous genotype, it is only used in combination with the maximum tested doses of VX-659 and VX-445. The studies do not state why a combination of VX-561 is tested in these trials, or why it is only tested in people with F508del/MF genotypes, or why it is only tested in combination with the maximum doses of the above medications (151, 152).

When efficacy data was pooled, triple combination therapies were shown to have statistically significant improvement in QoL, relative and absolute change in FEV_1 and absolute change in sweat chloride from baseline (151, 152).

4.4.3 Quality of the evidence

Several studies in this review incorporated complicated study designs with multiple drug doses and genotype combinations. This reflects stringent regulatory requirements and the demanding processes needed to have a trial approved, therefore trialists may find it beneficial to get as much information from the same trial as possible. It can also reflect the desire to move quickly, to try & test the next step in treatment. The example of this here is the inclusion of a group of participants in both of the included phase 3 triple combination trials being allocated to take VX-659/445-tezacaftor-VX-561 as part of the same trial (151, 152).

4.4.3.1 Monotherapy versus placebo

The Horsley study of FDL169 was early phase, meaning there was limited outcome data and risk of bias was hard to judge (Tables 1 & 2) (160).

4.4.3.2 Triple combination therapy versus placebo or control

The early phase triple therapy trials were complex because they evaluated a number of factors; different doses, different genotypes (F508del/F508del and F508del/MF) and different forms of ivacaftor. This resulted in 8 different comparator groups.

For the phase 1 and 2 studies examining VX-659 and the phase 2 study of VX-445, we judged the quality of the evidence to be low to moderate. All domains of risk of bias were low, except for unclear risks of blinding of outcome assessment and selective reporting (Tables 3, 4 & 5). Some outcomes stated in the trial's methodology were not reported (safety measures). The GRADE assessment led to downgrading of evidence due to members of the review team judging there to be unclear methodological information on the blinding of outcome assessors and potential selective reporting. It was also downgraded due to the small number of participants and the studies being conducted over a short timescale leading to possible imprecision of results. A further downgrade was justified due to lack of applicability of results as there is no data for children with CF or people with more severe disease(152, 160) (Summary of findings tables can be found in the appendices).

4.4.4 Potential biases in the review process

A comprehensive literature search using the Cochrane Cystic Fibrosis and Genetic Disorder Review Group's register of CF trials and ongoing trials was conducted. Journal conference abstracts were also searched. Once searching was complete, two authors (JM & IS) individually judged the eligibility of results using the pre-determined inclusion and exclusion criteria. Studies that were eligible for inclusion had their data extracted independently by the same two authors, using a data extraction form that had been made beforehand. They also independently assessed risk of bias for each included study. Where any disagreement arose, a third author provided arbitration. Analysis of the data was also performed by JM & IS authors, using the Cochrane Review Manager software (194). Data analysis was also checked by the review's statistician. This adherence to Cochrane methodology aimed to minimise the risk of bias throughout the processes of the review.

This systematic review used all available published data. Authors of the studies were contacted for unpublished information and data on individual participants, but as of yet, no further data has been supplied.

4.4.5 Agreements and disagreements with other studies or reviews

We are not aware of any already published reviews of triple combination therapy for people with CF with at least one class II variant. However, during the writing process of this systematic review, we were made aware of a review and meta-analysis examining dual-combination therapy (195) (as the previous edition of this systematic review did). We therefore decided to read and appraise this review for comparison:

The review, written by Wu et al. and published in December 2018 examined efficacy and safety of dual combination of *CFTR* correctors and potentiators (monotherapy was not assessed). It looked at people with CF with F508del/F508del. Two studies included in this Cochrane Review were not included in the Wu review, although they did meet the eligibility criteria (169, 170). Also, for another dual combination study, the previous version of our Cochrane review included data from its cohort 1, but not cohorts 2 and 3 due to concerns over pooling the control group (161); the Wu review includes these data. Furthermore, our review only included heterozygous participants from the Donaldson 2018 tezacaftor-ivacaftor study, due to other participants being pooled which negated the effects of randomisation (100). The Wu review includes all pooled and unpooled participants (including those not homozygous for F508del). Consequently, the total number of participants and results are different to those found in this Cochrane Review. The Wu

review presents a meta-analysis of efficacy data for both lumacaftor-ivacaftor and tezacaftor-ivacaftor therapies; however, we considered the interventions to have different mechanisms of action and hence did not combine the data. Finally, Wu did not report the adverse event of hypertension found with lumacaftor-ivacaftor therapy which we reported. In our opinion, the conclusions of the Wu review are not supported by their meta-analysis and overstate efficacy measures. In addition, the authors claim to demonstrate a dose-response effect, but there is no evidence of this from the data presented. Much of the interpretation within the Wu review seems to be based on observational and "experimental" studies not actually included in the review, rather than evidence from their meta-analysis.

4.5 Conclusions for Cochrane systematic review

4.5.1 Implications for practice

Currently, there is no evidence to support monotherapy correctors for people with cystic fibrosis with either F508del/F508del or F508del/minimal function genotypes.

There are no new data on dual combination therapies to influence the conclusions presented for dual combinations in the previous version of this systematic review (99).

Early phase studies for triple therapy combinations demonstrated an acceptable safety profile and tolerability with significant improvements in respiratory function and quality of life compared to placebo or control over four weeks in people (F508del/F508del and F508del/MF) with mild to moderate lung disease. The magnitude of the reported improvements in efficacy measures suggest the potential of these agents to provide a significant intervention for people with CF (F508del/F508del), but phase 3 study data are required before these agents can be recommended for clinical practice.

4.5.2 Implications for research

Post-market surveillance should continue for all of the mentioned therapies. Tezacaftor-ivacaftor (which forms components of the new triple therapy regimens) appears so far to not have resulted in the adverse events recorded with lumacaftor-ivacaftor, however data on its safety in children is required, as well as long-term monitoring.

It should also not be automatically assumed that these therapies have the same efficacy for various different type II variants (e.g. G85E). The pathway from the endoplasmic reticulum to the cell surface membrane are complex, and different problems to those seen in F508del may affect the trafficking of other *CFTR* variants. It is unclear whether correctors will prove

effective for people with type II variants other than F508del and this should be investigated. However, the smaller numbers of people with CF with these variants will make conducting studies in this population a challenge.

It is positive that both F508del/F508del and F508del/minimal function genotypes have been included in the latest triple therapy trials. Continuation of this inclusive approach in future trials should be encouraged.

Also, with future studies, methodology should be clearly reported to reduce risk of bias; for example, the randomisation and blinding processes, as well as maintaining randomisation during data analysis to avoid loss of randomisation during pooling of some results.

With previous concerns raised about adverse events in some of these therapies, reporting of safety and adverse events in novel treatments is paramount and should be conducted consistently and comprehensively.

5. A study of clinical outcome measures in trials for pre-school children with CF

5.1 Introduction

5.1.1 Background

There is currently no agreed COS for pscwCF. Creation of a core outcome set will increase quality of trials in this age group, improve validity of meta-analyses and provide more meaningful information for all stakeholders involved in the care of pscwCF.

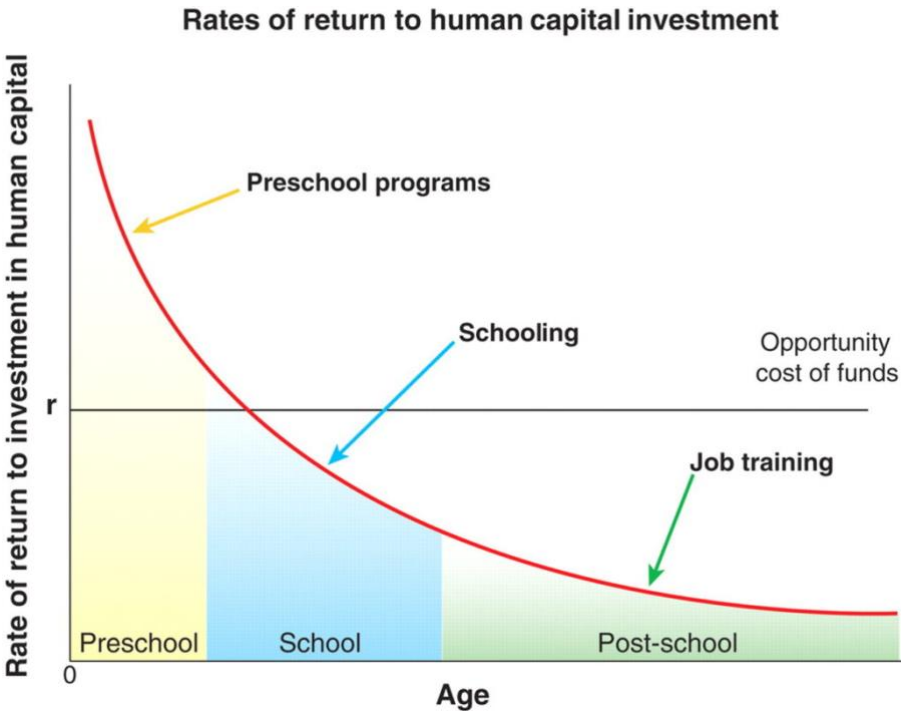

***Figure 10**: Skill formation and the economics of investing in disadvantaged children. Heckman JJ. Science. 2006 Jun 30;312(5782):1900-2 (196)*

It has been shown that early intervention leads to benefits of a greater magnitude in the future. Though not specific to children with CF (figure 10 above examines investments to benefit disadvantaged children), Heckman highlights the increased value of positive input early in a child's life versus leaving the same measures until later in a person's life. This same principle applies to pre-school children with CF and highlights just how important it is to ensure the best outcomes are measured during the pre-school years (196). An example specific to CF is shown in a retrospective observational study by Dijk et al., which compared outcomes in a group with CF detected through newborn screening, compared to a historical

control group who were not screened. The screened cohort (with earlier intervention) had slightly better growth and lung function, lower pseudomonas acquisition and better survival (see figure 11 below) (197). Small changes in the early years led to large differences in survival, a phenomenon similar to that of the Heckman curve which reaffirms the message that high quality benefits at an early stage will make large, lasting benefits in the future, which is what makes creation of a COS for pscwCF an important aim. The challenge of clinical trials in pscwCF is identifying meaningful outcomes and performing sufficiently powered studies to detect the small differences which will likely be important in early adult life.

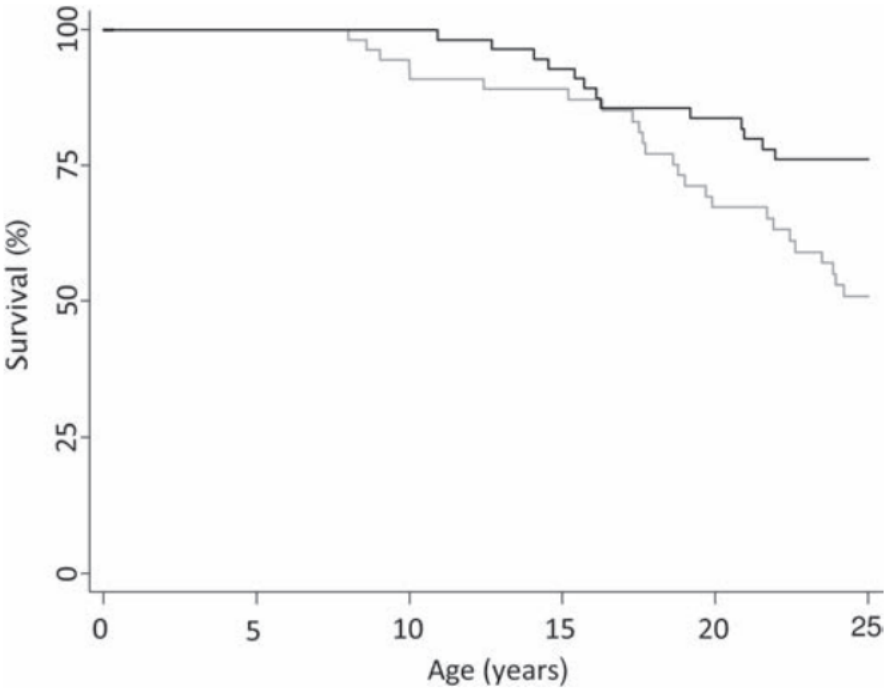

***Figure 11**: Kaplan-Meier survival plot of screened (dark line) versus non-screened (grey line) people with CF from Dijk et al. (197)*

Further beneficial applications of a COS include the fact that they allow us a standardised measure of the progress a child and their family is making by tracking the outcomes which we would know are the most important markers or measures of their wellbeing and happiness over time. A COS may also improve access to new therapies, as we could have a better knowledge of which outcomes matter most when evaluating medicines, improving rapid access to new therapies for pscwCF. Additionally a core outcome set can contribute towards comparative effectiveness research, where different investigations, interventions and their benefits and risks are compared (198). A COS allows us to consistently measure outcomes to determine which intervention provides the greatest benefit and least risk.

To produce a robust COS requires rigorous preliminary work and methodology. The first step of this is to review the current state of outcome reporting in this group. Monitoring for safety is typically similar throughout trials, with recording of adverse events during the trial and through post-market surveillance afterwards, with awareness of the possibility of 'unknown unknowns'. Efficacy related outcomes can differ considerably depending on the condition being included, the demographics of participants and the intervention being tested.

5.1.2 The distinct challenge and need for a COS in pscwCF

There is currently no core outcome set for pre-school children with CF. Fewer clinical trials are conducted in pscwCF when compared to those who are older. It is therefore imperative to improve the quality and consistency of trials. This would lead to a higher yield from research for all stakeholders and improve the outlook for pscwCF in the future. It is also not ethical to ignore this group when previously existing work on core outcomes does not adequately address their needs or challenges.

A core outcome set would help facilitate a higher quality trial that is more valuable to all stakeholders involved in the care of pre-school children with CF.

A similar review published in 2016 searched for primary research (not just RCTs) in pscwCF. It examined three outcomes: 1) At what age have CF-related dysfunction and structural differences been shown in pscwCF? 2) At what age has progression of disease been demonstrated in pscwCF? 3) At what ages does early versus late intervention show improved outcomes in pscwCF? As part of its search strategy, it found that a low proportion of primary research in people with CF was conducted in preschool children. In this small proportion of research, a large number of measures relating to current disease state were reported (199).

5.1.3 Aim

Review and collate which outcome measures are reported in high quality RCTs including 0-5 year old children with CF in their study population. To identify high quality trials, we interrogated the Cochrane library of reviews and trials.

5.2 Methods

5.2.1 Outcomes to be measured:

1. Frequency of what efficacy outcomes are measured by the systematic reviews, and their included trials.
2. Quality of trials in this age group- risk of bias analysis for the included RCTs (not systematic reviews)
3. Do the systematic reviews and trials examine exclusively pscwCF, or older children or adults as well?

5.2.2 Eligibility criteria:

For both Cochrane systematic reviews and RCTs:

- Examine an intervention
- Reported outcomes include those relating to efficacy of the intervention

For Cochrane systematic reviews:

- To include randomised controlled trials which included 0-5 year olds with CF as part of their recruited study groups

For randomised controlled trials:

- To be included in a Cochrane systematic review
- To include a process of randomisation
- To include a control group
- Panel decision during information gathering: recruited study population to consist exclusively of 0-5 year olds.

Another component of this work is a Cochrane systematic review, an example of high-quality literature and comprehensive data searching. It was therefore decided that Cochrane reviews would provide an ideal source of trials as a sample to represent the state of outcome reporting in this age group.

5.2.3 Identifying eligible papers:

The Cochrane Library of systematic reviews was searched using the term 'cystic fibrosis' on 8th October 2018.

Each Cochrane review in the search result was initially screened by title, then abstract, then full paper if necessary. Once this was completed, for each of the Cochrane reviews which were eligible so far, their 'characteristics of included studies' sections were examined to check for trials which included 0-5 year olds, and also that they were randomised, controlled trials. In the case that this information was not provided in the 'characteristics of included trials', the full versions of the trials in question were obtained and checked for this information. If there was uncertainty as to whether a given trial included participants aged 0-5, it was excluded, meaning its respective Cochrane review may also be excluded, should it not include any other eligible trials.

Once eligible Cochrane systematic reviews were identified, each of their included trials were again screened by title, abstract and full text where necessary, according to the above eligibility criteria.

The panel excluded a number of the Cochrane reviews concerned with interventions that are not appropriate for 0-5 year olds with CF.

A decision was also made as a panel to include randomised controlled trials which exclusively included 0-5 year olds as their study population. This was partly due to the finding of several trials including a very small number of participants, often just one participant in our eligible age group of 0-5 year olds, with the remainder being older children or adults. As a panel we felt this did not make for the best reflection of outcomes reported in pre-school children with cystic fibrosis. Although outcomes from these "wider" studies will be compared to this group of outcomes in future work.

5.2.4 Data extraction

For eligible reviews and trials, we attempted to retrieve a published protocol. This was possible for all but one Cochrane review, where the Cochrane cystic fibrosis & genetic disorders group was contacted, who recommended we use the methodology in the first version of the review itself, as the closest available approximation to the protocol. Protocols for included trials were searched for, and their respective authors contacted. Two authors replied.

5.2.5 Themes of outcomes

Also at this stage, the panel grouped each of the eligible reviews and trials into one of the following predetermined themes, relating to different areas of treatment for CF:

1. Managing CF airways disease
   -Antibiotics
   -Airway clearance/physio
   -Aerosolised therapies
   -Other
2. Managing CF nutrition
3. Managing CF liver disease
4. Other

Outcomes were extracted from protocols (where available), methodology, and results sections. This was with the intention in the future to assess both the outcomes which trials and reviews say they will examine and compare this with the outcomes they report in results.

Outcomes were initially recorded as a list for each review and trial, with the frequency of which that each outcome was listed then being counted and recorded. The frequency recorded corresponds to the number of reviews/trials which state or report this outcome in their respective protocol, methods or results. A separate list was made and count was performed for first the Cochrane reviews, and then for the randomised controlled trials.

Once outcomes were counted and recorded, they were also grouped into themes. It was found that the themes for the papers didn't best transfer to individual outcomes, and so a more applicable set of themes were devised by the panel, which reflected different components of treating and monitoring someone with CF:

1. Airway
2. Extra thoracic disease
3. Patient/parent reported outcomes
4. Nutrition
5. Microbiology
6. Other

In addition to our own themes, we also classified the outcomes into the COMET initiative's taxonomy (100):

1. Death
2. Physiological/clinical
3. Life impact
4. Resource use
5. Adverse events

We then counted the number of outcomes in both our themes, and COMET themes.

Some of the outcomes stated fitted into two COMET themes, and hence were counted under both themes.

5.2.6 Risk of bias

All included trials also had their risk of bias evaluation checked. This was used as a marker of the quality of included trials. All included trials had a risk of bias evaluation already performed and available within their respective Cochrane reviews. If this was not the case however, we would have performed the same risk of bias evaluation as used in the Cochrane process (153).

The rule for deciding overall risk of bias was:

One or more category showed unclear risk of bias = overall unclear risk of bias

One or more category showed high risk of bias = overall high risk of bias

If all categories were low risk of bias = overall low risk of bias

5.3 Review of outcomes- results

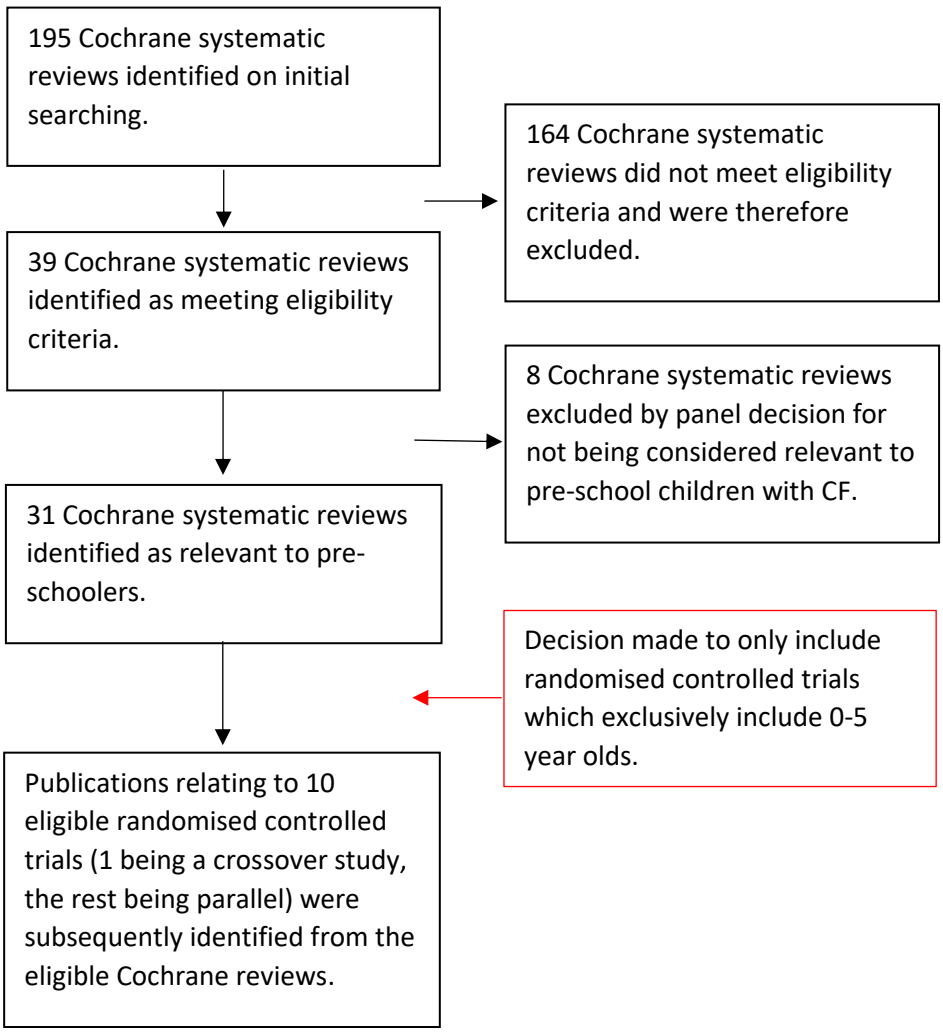

***Figure 12**: PRISMA flowchart showing results of search and eligibility assessment*

31 Cochrane systematic reviews and 10 randomised controlled trials went on to data extraction.

5.3.1 Frequency of what efficacy outcomes are measured by the systematic reviews, and their included trials.

In the count of outcomes reported by the included Cochrane systematic reviews, 139 different outcomes were reported in at least one of the protocol, methods or results sections of at least one of the included papers.

5.3.1.1 Breakdown of findings from systematic reviews:

Protocol stage:

Protocols were available for 30/31 included Cochrane systematic reviews. For the one review whose protocol was not available, we first attempted to locate the protocol. After this was unsuccessful, and following advice from the Cochrane CF & Genetic Disorders Group, we elected to identify the outcomes stated in the methods section of the earliest draft version of this review, which is available on Archie, Cochrane's review archive site, as this was the first piece written following the protocol and would most closely resemble its methodology.

For COMET themes and the frequency of their included outcomes, it is important to remember that several outcomes have been classified under two different COMET themes, and have therefore been counted in both themes.

	Protocol		Methods		Results	
	Number of different outcomes in each theme	Total frequency that outcomes in this theme are reported	Number of different outcomes in each theme	Total frequency that outcomes in this theme are reported	Number of different outcomes in each theme	Total frequency that outcomes in this theme are reported
CF Theme						
Airway	25	102	25	106	18	88
Extra-thoracic disease	16	16	17	17	14	14
Patient/parent reported outcomes	5	28	5	31	3	26
Nutrition	9	37	11	37	10	33
Microbiology	18	71	17	85	17	73
Other	21	103	23	120	20	121
Total	94	357	98	396	82	355
COMET theme						
Death	2	18	2	18	2	19
Physiological/clinical	70	223	73	239	63	214
Life impact	7	39	9	45	7	41
Resource use	13	52	13	65	12	59
Adverse events	12	35	14	40	11	37
Total	104	367	111	407	95	370

***Table 7**: Number of different outcomes reported under each CF-specific theme and COMET theme and the total frequency of outcomes reported under each theme for the protocol, methods and results stage of included systematic reviews.*

5.3.1.2 Breakdown of findings from randomised controlled trials

Protocol stage

Despite efforts to contact the authors of every included trial, only 2/10 authors replied to provide the protocols for their respective trials. It was therefore decided that this provided an insufficient amount of data with which to add meaningful information to our analyses and conclusions. We therefore decided to focus on the methods and results sections of the included randomised controlled trials. Should we receive more protocols in the future, this may allow the protocols of these trials to be included in further analysis.

Methods & results stages

	Methods		Results	
	Number of different outcomes in each theme	Total frequency that outcomes in this theme are reported	Number of different outcomes in each theme	Total frequency that outcomes in this theme are reported
CF Theme				
Airway	12	15	17	36
Extra-thoracic disease	6	6	5	6
Patient/parent reported outcomes	2	2	3	4
Nutrition	7	15	5	15
Microbiology	13	23	16	26
Other	20	36	19	40
Total	60	97	65	127
COMET theme				
Death	1	1	3	3
Physiological/clinical	52	80	54	97
Life impact	4	5	7	10
Resource use	7	12	7	19
Adverse events	2	6	2	6
Total	66	104	73	135

***Table 8**: Number of different outcomes reported under each CF-specific theme and COMET theme and the total frequency of outcomes reported under each theme for the methods and results stage of included randomised, controlled trials.*

5.3.2 Quality of trials in this age group- risk of bias analysis for the included RCTs (not systematic reviews)

Trial	UK' 91 screening	Wisconsin '98 screening	Button '03	Doumit '12	Stutman '02	Gibson '03	Wainwright '11	Rosenfeld '12	Cohen '05	Costantini '01
Adequate sequence generation?										
Allocation concealment?										
Blinding? All outcomes										
Incomplete outcome data addressed? All outcomes										
Free of selective reporting		Not in risk of bias table								
Free of other bias										
Overall risk of bias										

Table 9: *Risk of bias assessments, including overall risk of bias, for all included RCTs. A larger version is available in the appendix.*

5.3.3 Do the systematic reviews and trials examine exclusively pscwCF, or older children or adults as well?

As mentioned in the methods, a decision was made to only use randomised controlled trials which exclusively included participants in the 0-5 year old age group. This was due to many previously eligible trials containing just one or very few 0-5 year old which led to the panel deciding that to include trials exclusively examining the age group of interest would give a better representation of outcomes reported in pre-schoolers with CF.

5.4 Discussion of study of outcomes in pscwCF

The low number of trials, the majority of which had high or uncertain risks of bias, combined with the large variety of outcomes and their themes highlight the difficulty in conducting research in young children and in identifying what are best outcomes to consider as part of this research. A disproportionately high number of outcomes were short-term, surrogate biomarkers which gave a snapshot of disease state/condition of the person at that time. A considerably smaller proportion of outcomes reflected the longer term, lived experience for children and their families. Some established outcomes such as FEV_1 and similar are generally agreed to not provide valuable information for pre-school children. It is difficult for a child of pre-school age to perform tests such as spirometry in such a way that they give reliable information. Regardless of this consideration, such outcomes were measured and reported by included trials more frequently than those longer-term patient-centred outcomes. For example, FEV_1 was reported in the results of 5/10 trials, whereas quality of life was reported in the results of 1/10 trials. Other short-term measures were regularly recorded, for example FEF 25-75 (forced expiratory flow at 25-75% of the pulmonary volume) was reported in the results of 6/10 trials. Other, more recent methods of representing current disease state, such as lung clearance index (LCI) were stated by 6 of the included systematic reviews, but not reported by any included trial. This could be due to included trials testing interventions not related to airways disease, or the trials being performed and published before these more recent investigations became as accepted as they currently are as we did not set a time limit as part of our eligibility criteria. It is not necessarily bad that numerous surrogate outcomes are measured, as many may provide useful information. However it is also important to highlight that other, pragmatic outcomes can also give useful information and may be under-represented by trials.

A total of 65 different outcomes were reported in the results of the included RCTs. Considering the example of airway measures (one of the CF themes proposed by the research team), 17 different outcomes were reported. 16 different outcomes related to microbiology were reported. This large number of outcomes can increase variability between trials. This makes meta-analysis more difficult.

This work can serve to highlight the need for more trials to be conducted in this age group, as well as the importance that these trials must be of as high a quality as possible. Creation of a core outcome set will provide guidance on those considering performing research with

this group. It will also lead to improvements in the quality of this research and the value of its conclusions which can be drawn upon by many, if not all stakeholder groups. A core outcome set can also encourage the use of both novel investigations and tried & tested investigations of value, whilst discouraging the measurement of less useful information. The standardisation of outcome reporting could reduce heterogeneity and allow for improved incorporation into systematic reviews and meta-analyses.

Limitations of this work: This review used the Cochrane library of systematic reviews as its source to identify firstly relevant Cochrane systematic reviews and subsequently randomised controlled trials. A possible limitation of this work is that non-Cochrane systematic reviews which otherwise meet our eligibility criteria may therefore not have been identified by our search strategy. This may in turn mean that some RCTs which may have provided useful information may also not have been included. Additionally, it should be acknowledged that forms of research other than RCTs, for example cohort studies, may have also provided valuable information on outcomes for pre-school children with CF. Although this work is not itself a Cochrane review, it uses them as a source of information and thus reflects their methodology. Cochrane reviews often specify the design of included studies must be RCTs, meaning they exclude other study designs, again such as cohort studies. Though this means that Cochrane reviews and therefore this study identify what is typically considered the gold standard of primary research, they may miss studies which may still be conducted to a high standard and provide useful data. As Cochrane reviews are expected to have a comprehensive search strategy which identifies all studies meeting its eligibility criteria, there should not be an issue of eligible studies not being identified by Cochrane systematic review search strategies.

We also found that many of the included Cochrane reviews stated that if there was no data found for an outcome which they had pre-specified to report on, they would not report this outcome. Some reviews still reported these outcomes and stated that no data were available. Other reviews however did not specify that no data were available and instead simply did not include/report upon this outcome. This meant it was sometimes not possible for us to distinguish between whether there was simply no data for these outcomes, or whether any selective reporting bias was present within the included Cochrane systematic reviews.

Additionally, we evaluated quality by means of risk of bias. Other tools relating to quality of evidence, such as GRADE could have been used, this additional quality appraisal could be

performed for future publication of this work, to further increase the robustness of its findings and conclusions.

The next steps toward creating a core outcome set for this group will involve making contact with many stakeholder groups to seek their involvement and contribution towards a Delphi survey (as described above), followed by a group consensus study to identify that optimum set of outcomes. Once this is done however, the process is not complete. Core outcome sets can be continually reviewed and improved over time as new investigative tests emerge, priorities of preschool children with CF and their families change or provision of services alters.

6. Discussion

6.1 Summary and implications

There is no evidence to support the use of corrector monotherapy in people with CF with at least one copy of an F508del variant. We await the results of trials testing novel correctors in monotherapy e.g. GLPG2222 (189, 190).

No new trials testing dual combination therapies were identified by this review. Tezacaftor/ivacaftor remains the dual combination standard of care for those with CF who have two copies of F508del as it shows similar efficacy to lumacaftor/ivacaftor in statistically significant improvements in respiratory function, but without the significant adverse events and less desirable pharmacological properties of lumacaftor. No new data was provided for dual combination therapies for people with CF with one copy of F508del and another variant, such as a minimal or residual function variant. In the triple therapy trials, tezacaftor-ivacaftor was used as the standard of care for the control group in participants with 2 copies of F508del. For the triple therapy trials examining impact on F508del/minimal function patients, a triple placebo was given.

This is the first systematic review of triple combination *CFTR* modulator therapy. Triple therapy (in a number of different combinations) resulted in statistically significant improvements in two of the review's three primary outcomes of quality of life and pulmonary function in people with CF aged over 12 years with either one or two F508del variants. The third outcome, survival, was not analysed by the included triple combination trials. The improvements seen were similar in magnitude to those seen in trials testing ivacaftor in people with CF with type III variants (151, 152).

These results suggest that a significant pharmacological therapy may be available to people with CF with at least one copy of an F508del variant. Triple combination therapy is still in trial stages; however it may soon be available outside of trials. Currently the most recently approved regimen for people with CF with 2 copies of F508del variants is dual combination tezacaftor-ivacaftor, however this is only currently available in 4 countries, Denmark, Germany, Iceland and The Republic of Ireland. Lumacaftor-ivacaftor is available in 10 countries, including the UK (200), where it is used through a managed access scheme for patients with poor condition. The manufacturer of these drugs produced a press release on 31st May 2019 stating that they had chosen to submit VX-445 (named elexacaftor) in triple combination with tezacaftor-ivacaftor for global regulatory approval (201). They have not

chosen to do the same with VX-659. This decision is based on phase 3 trials that have not been published and were not available for this review. The summary data in the press release suggest a similar magnitude of effect to that outlined in this review from the phase 2 trials.

Triple therapies may form the next major step in treating people with CF with one or two copies of F508del. These combinations must be carefully evaluated for safety and efficacy, especially in children and young people, including in pscwCF. In this age group, the most appropriate outcome measures must still be determined.

The phase 2 trials included an arm that examined VX-561 (deuterated ivacaftor) at a once daily dose instead of ivacaftor. Our forest plot suggests this regimen resulted in as good a response, if not a greater magnitude of improvement than the triple combination with normal ivacaftor (figures 6 to 9). This drug was likely tested as part of the same trials in order to allow it to pass through approval and trial processes quicker (202). Included trials only tested VX-561 in participants with F508del/MF genotypes. It should also be tested in homozygous people and in children. Despite the positive results and the once per day dosing, VX-561 has not yet been submitted for regulatory approval.

The cost of these therapies is currently high, and this may limit access for many people with CF who could benefit from them. The health technology assessment undertaken in the UK for lumacaftor/ivacaftor did not result in approval. If for example, triple therapy was approved for use in the UK, and if we assume it costs similar to that of ivacaftor quoted by the BNF as £500 per day, then according to the CF trust's latest registry report, 8834 people with CF may be eligible for these medicines in the UK (4852 F508del/F508del, 3982 F508del/Other variant) (203). If all of these people start the medication, then the yearly cost to the NHS would be £1,612,205,000 (£1.6 billion). In 2017/18, the NHS' total budget for the year was £124.7 billion (204).

6.2 Trials & outcome measures in trials of pscwCF

For most CF studies, absolute change in FEV_1 is the primary outcome measure. Measures of pulmonary function are challenging in pscwCF. Recent studies in pscwCF have used multiple breath washout technique to measure lung clearance index (LCI). Following use as a secondary outcome measure in the ISIS study and promising data (145, 205), the SHIP (Inhaled hypertonic saline in pre-school children with CF) RCT published June 2019 employed $LCI_{2.5}$ as its primary outcome as the investigators felt it can give more valuable information than previous conventional pulmonary function tests in this age group. LCI is a time-consuming investigation that still requires cooperation from the child and skilled investigators. The SHIP study demonstrated a significant reduction in LCI in children receiving twice daily hypertonic saline compared to children receiving normal saline. Commentators considered this to be an intervention that should be considered for all pscwCF, but this needs to be balanced against the addition in treatment burden (72, 73).

The James Lind Alliance, an initiative which consults stakeholders to determine the priorities for research in a specific condition which they want addressed, these are called priority setting partnerships (PSPs). The PSP for people with CF found treatment burden was considered the most important priority to address (the full PSP top 10 priorities list can be found in the appendix) (206). People with CF and stakeholders may find it very valuable if trials reported upon endpoints examining the impact on treatment burden. The new triple combination *CFTR* modulating therapies and future therapies may play an important role in reducing treatment burden; but as of now trials of these new combination therapies are not considering this outcome. A retrospective analysis of people with CF with a G551D variant taking ivacaftor monotherapy found that over two years of ivacaftor treatment there was a statistically significant decrease in the prescription of azithromycin, dornase alfa, inhaled bronchodilators, inhaled corticosteroids and oral supplements. The decreases seen in hypertonic saline, inhaled antibiotics and pancreatic enzymes were not statistically significant (207). It is important to note that though statistically significant, this does not tell us whether the results were clinically significant and whether the participants felt their treatment burden had improved. The age range of this analysis was from age 6 to 51, median age 17; therefore these results may not directly transfer to pscwCF but are still valuable.

Our study of outcome reporting found that trials in pscwCF reported a wide variety of outcomes and these outcomes were predominantly surrogate markers giving a short-term measure of disease activity. There was a lack of validated measures of the direct impact of

CF on a child and their family, as well as markers of longer-term wellbeing. This agrees with the similar review mentioned in section 5.1.2 (199). There are lots of modalities of trying to detect pathology, but it is difficult to know which measures are the best in this age group, as pscwCF are generally well, may not be cooperative and as a result it is difficult to perform investigations to give a valid result. Although we may be able to detect presence of, or change in disease state, we may not know if this translates to a meaningful difference in the wellbeing of the child with CF and their families. This similar review also found very few pragmatic outcomes directly relating to the current and longer term wellbeing of the child & family (199). As this other review looked at various forms of primary research, not just RCTs, this can show that the lack of these pragmatic outcomes is not exclusive to RCTs and is an issue throughout research in pscwCF.

The design of trials can have an important impact on the value of results, for example in the KIWI study (and its extension, KLIMB), which were open label single arm studies of ivacaftor in pscwCF aged 2-5 years. A rise in liver function tests was observed in 30% of participants by the end of KLIMB (120, 208). The lack of a placebo group means it is difficult to reliably say whether this was an adverse effect of the test intervention or reflective of the normal natural history for pscwCF.

Our Cochrane review included outcomes such as: number of admissions and days spent in hospital, measures of attendance at work/school. These are important outcomes which play a role in reflecting the ability to live as 'normal' a life as possible. None of the new trials in this review include such outcomes, but they are phase 2, short term studies. Since completion of this systematic review, both VX-659-tez-iva and VX-445-tez-iva are awaiting release of phase 3 study results and an open label extension has been announced for both VX-659-tez-iva (ECLIPSE) and VX-445-tez-iva (AURORA) (209). The rationale for these studies states that the studies will include participants age 12 and older and will not include younger children (209). The primary outcome will be absolute change in percent predicted FEV_1 and they will include CFQ-R respiratory domain and pulmonary exacerbations (both number of and time to) as part of their secondary outcome analyses. Outcomes such as school attendance, time spent in hospital etc. are not recorded in the protocol. They will also include safety over a longer time period (24 week study period followed by 96 week open label extension) (209). Earlier phase trials have not yet been initiated to assess safety in younger & preschool children. They could therefore not be included in this longer-term study despite what we already know that younger children have the potential to get the greatest magnitude of benefits over the long term from such interventions. Once safety is

established in older participants, more focus should be placed earlier on the assessment of safety of these therapies in young children; followed by if they improve & extend the lives of these children and their families, and by what magnitude. A COS would improve the likelihood of this occurring.

6.3 Future work

The Cochrane systematic review will again need updating in the near future to keep pace with the new corrector therapies being tested and results from the phase 3 triple therapy trials, once published. Future versions of this review can also include an assessment of cost-effectiveness of therapies.

The work reviewing outcomes in pscwCF will be produced as a paper and submitted for publication. Included in this report will be an analysis of selective reporting bias in these trials; essentially recording all outcomes measured as stated by published protocols and comparing those to the outcomes that are actually reported once the trial is completed. Formation of a core outcome set will require stakeholder engagement through Delphi consensus study to generate agreement on an initial core outcome set.

7. Conclusion

Corrector medications, when used in combination therapy with a potentiator, has the potential to make substantial improvements to the wellbeing of people with CF with at least one copy of a F508del *CFTR* variant. The latest combinations of therapy require testing in children, including pscwCF. A core outcome set would provide more consistent and meaningful outcomes for all stakeholders involved in the care of pscwCF.

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Appendices

BNF

In Confidence

YellowCard

COMMISSION ON HUMAN MEDICINES (CHM)

It's easy to report online at:
www.mhra.gov.uk/yellowcard

MHRA
Regulating Medicines and Medical Devices

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See `Adverse reactions to drugs' section in BNF or **www.mhra.gov.uk/yellowcard** for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials:_____ Sex: M / F Is the patient pregnant? Y / N Ethnicity:_____

Age (at time of reaction):_____ Weight (kg):_____ Identification number (e.g. Practice or Hospital Ref):_____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome

- Recovered ☐
- Recovering ☐
- Continuing ☐
- Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped: _____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- ☐ Patient died due to reaction
- ☐ Life threatening
- ☐ Congenital abnormality
- ☐ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistent or significant disability or incapacity
- Medically significant; please give details: _____

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

It's easy to report online: www.mhra.gov.uk/yellowcard

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address:

Postcode: Tel No:

Email:

Speciality:

Signature: Date:

CLINICIAN (if not the reporter)

Name and Professional Address:

Postcode: Tel No:

Email:

Speciality:

Date:

Information on adverse drug reactions received by the MHRA can be downloaded at **www.mhra.gov.uk/daps**

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at: **www.mhra.gov.uk/drugsafetyupdate**

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

***Figure 13**: Example of MHRA yellow card for reporting adverse events in medications, as included in the British National Formulary book.*

Example data extraction sheet used for this update of Cochrane review

Continuous data

Outcome	Unit of measurement	Intervention group												Control group										Any other details e.g. p value	
Primary		F508del/minimal function						F508del/F508del			F508del/minimal function: VX-561			F508del/minimal function			F508del/F508del			F508del/minimal function: VX-561			pooled vx-561 and ivacaftor	
		vx445 50mg + tez/iva			vx445 100mg+ tez/iva			vx445 200mg+ tez/iva			VX-445 200mg +TEZ/VX-561			Triple placebo			Placebo + tez-iva			Triple placebo			intervention	placebo
		n	Mean	95% CI	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	n	Mean	95% CI	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	n	Mean	95% CI		n=42	n=20
1. Survival																									
2a. Quality of life- total QoL																									
2b. Quality of life- sub domains (CFQR resp)- less		10	20.3 SE: 4.8	10.8-29.9	22	17.6 SE:3.3	11.0-24.2	21	24.4 SE:3.3	17.8-31.0	21	With adjustment of baseline: 23.9 SI		12	3.1 SE:4.4	-5.6-11.8	7	4.4 SE: 4.7	-5.3-14.1	5			With adjustment of baseline : 11.1 S	24.15	7.05
3a. FEV1 relative change from baseline (percent		10	19.3 (SE: 4.2	-10.8-27.7	22	13.8 (SE:2.8	8.1-19.5	21	26.2 SE:2.9	20.4-32.0	21	percent predicted FEV1 relative cha		12	0.3 SE: 4.4	-7.8-8.3	7	1.4 SE 5.0	-9.0-11.8	5			percent predicted FEV1 relative cha	23.05	0.95
3b. FEV1 absolute values (litres)																									
Change in FEV1 absolute values (litres)		10	0.42 SD: 0.37		22	0.34 SD:0.25		21	0.53 SD:0.36		21	0.47 SD: 0.37		12	-0.04 SD:0.25		7	-0.01 SD:0.20			8	0.03 SD: 0.16		0.5	-0.035
Baseline FEV1 values (litres)			2.06 SD: 0.55			2.37 SD 0.85			2.12 SD: 0.89			2.20 SD: 0.73			2.50 SD: 0.79			2.80 SD: 1.06				2.18 SD: 0.66		2.16	2.34
3c. FVC relative change from baseline																									
3d. FVC absolute values																									
3e. LCI																									
3f. Other relevant physiological measures of lung function																									
Secondary																									
2a. Hospitalisation- number of days																									
2b. Hospitalisation- number of episodes																									
2c. Time to next hospitalisation																									
3. School or work attendance- days missed																									
4. Extra courses of antibiotics																									
a) time to next course																									
i) oral																									
ii) IV																									
iii) inhaled																									
b) total number of courses																									
i) oral																									
ii) IV																									
iii) inhaled																									
5. Sweat chloride change from baseline (least sq		50	-38.2 SE:4.2	-46.7, -29.8	52	-33.2 SE: 2.1	-38.9, -27.5	51	-39.1 SE:2.9	-44.9, -33.3	51	-33.6 SE: 2.1	39.4, -27.8	12	-2.2 SE:3.9	-9.9-5.6	7	0.8 SE:4.9	-9.3-11.0	5		1.0 SE: 4.6	-8.4, 10.3	-36.35	-0.6
6a. CXR score																									
6b. CT score																									
9. Nutrition & growth (relative change from baseline, including z scores of centiles)																									
9a. Weight																									
9b. BMI																									
9c. Height																									

Dichotomous data

	F508del/minimal function						F508del/F508del		All VX-445 groups (with normal ivacaftor)		F508del/minimal function: VX-561		F508del/minimal funct		F508del/F508del		F508del/minimal function: VX-561 subgroup		Pooled VX-561 + ivacaftor	
	vx445 50mg + tez/iva		vx445 100mg+ tez/iva		vx445 200mg+ tez/iva		vx445 200mg +tez/iva				VX-445 200mg + TEZ/VX-561		Triple Placebo		Placebo + tez-iva		Triple placebo		intervention	placebo
	n	%	n	%	n=21	%	n	%	n	%	n=21	%	n=12	%	n	%	n=8	%	n=42	n=20
Adverse effects (total)	10/10		21/22		18		19/21		68/74		19		12		5/7		7		18.5	9.5
i) mild	5/10		8/22		13		10/21		36/74		13		5		2/7		1		13	3
ii) moderate	4/10		12/22		5		8/21		29/74		6		6		2/7		6		5.5	6
iii) severe	1/10		5/22		0		5/21		3/74		0		1		1/7		0		0	0.5
7. acquisition of respiratory pathogens																				
a. Pseudomonas																				
b. staph aureus																				
c. h. influenzae																				
d. other clinically significant pathogen																				
8. Eradication of resp pathogen																				
a. Pseudomonas																				
b. staph aureus																				
c. h. influenzae																				
d. other clinically significant pathogen																				

Most common adverse events (incidence >5%) in vx445-tez-iva	F508del/minimal function						F508del/F508del		All VX-445 groups (with normal ivacaftor)		For this group, most common was classed as occuring in at least 2 patients F508del/minimal function: VX-561		F508del/minimal funct		F508del/F508del		For this group, most common was classed as occuring in at least 2 patients F508del/minimal function: VX-561			
	vx445 50mg + tez/iva		vx445 100mg+ tez/iva		vx445 200mg+ tez/iva		vx445 200mg +tez/iva				VX-445 200mg + TEZ/VX-561		Triple Placebo		Placebo + tez-iva		Triple placebo			
	n	%	n	%	n=21	%	n	%	n	%	n	%	n	%	n	%	n	%		
cough	4/10		5/22		7		10/21		23/74		5		1		1/7		2		6	1.5
increased sputum	3/10		4/22		5		8/21		20/74		3		3		2/7		1		4	2
infective exacerbation	3/10		5/22		2		5/21		15/74		3		4		1/7		4		2.5	4
haemoptysis	0		5		2		5		10				2		0				1	1
pyrexia	0		5		1		5		6				1		1				0.5	0.5
Nausea	2		3		1		1		7		2		2		1		3		1.5	2.5
Oropharyngeal pain	2		2		2		1		7		5		2		1		2		3.5	2
Headache	2		2		2		0		6				2		1				1	1
Nasal congestion	2		2		2		0		6		3		2		0		1		2.5	1.5
Nasopharyngitis	1		0		4		1		6				0		1				2	0
Increased creatine phosphokinase	0		0		1		4		5				0		0				0.5	0
Fatigue	1		0		0		4		5				4		0				0	2
Elevated aspartate aminotransferase	0		0		1		3		4				0		0				0.5	0
Diarrhoea	1		3		0		0		4				1		0				0	0.5
Respiration abnormal	0		1		1		2		4				0		0				0.5	0
Rhinorrhea	0		3		0		1		4				0		0				0	0
Productive cough											2						1		0	0.5
Chest pain											2						0		1	0
Paranasal sinus discomfort											2						0		1	0
Sinus congestion											2						0		1	0
URTI											2						0		1	0
Vomiting											0						2		0	1
																			0	0

More detailed information available on LFTs in supplement to article

Reported adverse events which cause interruption in vx445-tez-iva	Number of patients	
Elevated AST	1	
Elevated ALT	1	All the same patient
Elevated CK	1	
Myopathy	1	
Constipation	1	
Elevated bilirubin	1	

8% had abnormal ALT/AST (3x normal upper limit)
3% had raised bilirubin (2x upper normal limit)

Ongoing studies for Cochrane systematic review 2019

Monotherapy

Two studies are testing GLPG2222 (Bell 2017; Van der Ent 2018). One phase 2, placebo-controlled multicentre trial in Australia and Europe known as ALBATROSS is testing 150 mg daily or 300 mg daily of GLPG2222 for four weeks in 37 adults with CF with an F508del/Class III variant genotype who are already on stable ivacaftor regimens (188, 189). The outcomes they state will be reported include adverse events, pharmacokinetic data, concentration of sweat chloride, pulmonary function and quality of life. The second study, known as FLAMINGO and is also a multicentre phase 2 study taking place in North America and Europe (190, 191). This study is testing a range of doses of 50 mg to 400 mg four times per day of GLPG2222 for four weeks in adults with CF homozygous for F508del and a baseline FEV_1 of 40% predicted or more who have not taken other *CFTR* correctors in the previous four weeks. Stated outcomes include adverse events, sweat chloride concentration, pulmonary function, quality of life and pharmacokinetic data.

Two trials are studying PTI-428 (a class of *CFTR* modulator called an amplifier, which augments the actions of other *CFTR* modulators) (NCT02718495; NCT03258424). The first plans on recruiting 56 adults with CF (they do not specify class of variant) at 29 locations in Europe and North America (NCT02718495). The trial lasts 28 days of ascending doses (not stated) versus placebo. Stated outcomes include adverse events, pulmonary function, pharmacokinetics, sweat chloride concentration, weight and quality of life (NCT02718495). The second trial is a Phase I placebo-controlled RCT at two locations in the UK (NCT03258424). It is planning to recruit 16 adults with CF already taking stable ivacaftor for 14 days of treatment with adding PTI-428, of which the dose levels are not stated. Outcome stated include adverse events, pharmacokinetics, sweat chloride concentration, pulmonary function and weight (NCT03258424).

One phase 1 trials is studying PTI-801 both in monotherapy and in combination with PTI-428 versus placebo in adults with CF (homozygous for F508del in three cohorts and heterozygous F508del in one cohort) with a baseline FEV_1 of 40% to -90% and with a background therapy of lumacaftor-ivacaftor (193). It is a UK-based multi-centre study planning to enrol 32 participants, with treatment lasting 14 days with a follow-up visit at day 21. There are four arms, two 14-day arms comparing different doses of a combination of PTI-808 and PTI-801 against placebo, one 14 day arm comparing a triple combination of PTI-808, PTI-801 and PTI-428 versus placebo and one arm comparing PTI-808, PTI-801 and

PTI-428 to placebo for seven days followed by PTI-808 and PTI-801 versus placebo for a further seven days (with no washout period). Stated outcomes include adverse events, pharmacokinetics, pulmonary function, sweat chloride concentration, nutritional measures and quality of life.

One multicentre RCT is comparing 200 mg or 400 mg of a corrector known as (R)-roscovitine versus placebo in 36 adults with CF with either one or two copies of the F508del variant for three months (192). The primary outcome is safety with other outcomes including pharmacokinetics, quality of life, pulmonary function, body mass index, sweat chloride and nasal potential difference.

One week long trial is comparing glycerol phenylbutyrate (GPBA) as an oral liquid in a low-dose arm and in a high-dose arm against matched placebo in adults with CF, homozygous for F508del (NCT02323100). Stated outcomes include the adverse events, change in nasal potential difference, and sweat chloride concentration.

Dual combination therapy

Four ongoing trials are studying the safety and efficacy of tezacaftor-ivacaftor in people with CF; three trials are in people homozygous for F508del, one trial is phase 2 and multi-centre (NCT02070744), One is particularly studying chest imaging endpoints (NCT02730208) and one study is a multicentre parallel phase 3b RCT examining the safety, tolerability and efficacy of tezacaftor/ivacaftor in participants with CF aged 12 years plus who have previously taken lumacaftor/ivacaftor (NCT03150719). Another study is in heterozygous people with one copy of the F508del variant and one variant that is responsive to ivacaftor (NCT02412111). Another study is a parallel phase 3b parallel, multi-centre RCT in people homozygous for F508del who have previously taken lumacaftor-ivacaftor but discontinued due to an adverse event, with the aim of evaluating the safety and efficacy of tez/iva (NCT03150719).

Triple combination therapy

Three placebo-controlled trials are evaluating triple combination therapies, one is studying VX-152 in triple combination with tezacaftor/ivacaftor (NCT02951195), One is a first-in-human study of VX-445 conducted in people with CF who have either a F508del/MF genotype or A F508del/F508del genotype, as well as healthy participants without CF (NCT03227471).

A Phase 2 placebo-controlled study is assessing the efficacy of cavosonstat when added to pre-existing lumacaftor-ivacaftor therapy in adults with CF who are homozygous for the F508del-*CFTR* mutation (NCT02589236).

Risk of bias assessment tables for all remaining included studies in Cochrane systematic review 2019

Boyle 2014

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent party used a computer to create a random sequence.
Allocation concealment (selection bias)	Low risk	An interactive voice response system was used by pharmacists to dispense the medication.
Blinding of participants and personnel (performance bias)	Low risk	An independent pharmacist who was not masked prepared the doses of drug. The drug was then dispensed at each site by pharmacists who were masked to allocation. Placebo was matched in terms of number of tablets, their size, colour, packaging and coating.
Blinding of outcome assessment (detection bias)	Low risk	Study team at each site and sponsor of study were masked to both treatment assignment and sweat chloride concentration.
Incomplete outcome data (attrition bias)	Unclear risk	Data on a particular outcome for a participant was not included if it was insufficient. The example given is not including a participant's sweat chloride conc. data if an insufficient volume of sweat chloride was collected. It is unclear how excluding these data affects the balance of baseline characteristics between different participant groups.
Selective reporting (reporting bias)	Low risk	No selective reporting of outcomes was found following comparison of this trial's outcomes stated on clinicaltrials.gov (protocol not available) to outcomes reported in results.
Other bias	Low risk	Baseline characteristics were similar between groups.

***Table 10**: Risk of bias assessment table for Boyle 2014 (161).*

Clancy 2012

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Not enough information was given regarding how blinding of participants and study team was maintained.
Blinding of outcome assessment (detection bias)	Unclear risk	Not enough information was given regarding how blinding of outcome assessors was maintained.
Incomplete outcome data (attrition bias)	High risk	Total number of participants that was stated in adverse events table (n=45) is less than total number who were randomised (n=89). Figure 1B concerns change from baseline of sweat chloride, it states 63 participants were analysed. This is less than the total number of participants randomised to the intervention (n=72). There is a table of results for CFQ-R scores where 1 participant is missing from each treatment group.
Selective reporting (reporting bias)	High risk	$FEF_{25-75\%}$ and FVC were stated as outcomes but were not reported in results.
Other bias	Low risk	Baseline characteristics were generally well matched except for those in the 25 mg and placebo groups with less severe lung disease.

***Table 11**: Risk of bias assessment table for Clancy 2012 (162).*

Donaldson 2014

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Low risk	Participants, investigators, outcome assessors and care providers were all masked to intervention. Matched placebo was saline given at same volume as the intervention drug.
Blinding of outcome assessment (detection bias)	Low risk	Participants, investigators, outcome assessors and care providers were all masked to intervention. Matched placebo was saline given at same volume as the intervention drug.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for. All completed follow up at seven days.
Selective reporting (reporting bias)	Unclear risk	A full text of this trial was not available. Results are limited to those available on clinicaltrials.gov and do not have accompanying statistical analysis. It is unknown if any relevant information has been omitted.
Other bias	Low risk	Small numbers in groups but baselined characteristics appear balanced.

***Table 12**: Risk of bias assessment table for Donaldson 2014 (163).*

Donaldson 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Low risk	More information would be useful, however judged as likely low risk due to being a double blind, placebo-controlled study.
Blinding of outcome assessment (detection bias)	Low risk	More information would be useful, however judged as likely low risk due to being a double blind, placebo-controlled study.
Incomplete outcome data (attrition bias)	Unclear risk	2 participants have not been accounted for as part of analysis; however it is judged unlikely to have affected result.
Selective reporting (reporting bias)	Low risk	All outcomes have been reported, but at other time points which have not been reported such as day 7 & 14.
Other bias	Unclear risk	Gender imbalance- approx. two thirds of participants were female, but in the 200 mg twice daily group, there was a larger proportion of males. It is not known if these imbalances may have affected results.

***Table 13**: Risk of bias assessment table for Donaldson 2017 (164)*

Donaldson 2018

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Low risk	Double blind randomised controlled trial. Uses a matched placebo.
Blinding of outcome assessment (detection bias)	Low risk	Double blind randomised controlled trial. Uses a matched placebo.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for in analysis.
Selective reporting (reporting bias)	Low risk	All outcomes stated are reported
Other bias	Unclear risk	Small numbers of participants across groups has led to imbalance of baseline characteristics- unclear if this has affected results.

***Table 14**: Risk of bias assessment table for Donaldson 2018 (100)*

McCarty 2002

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Not enough information was given on how participant or study team were blinded and how this blinding was maintained.
Blinding of outcome assessment (detection bias)	Unclear risk	Not enough information was given on how outcome assessors were blinded and how this was maintained.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for.
Selective reporting (reporting bias)	Low risk	Outcomes reported in results were the same as those stated in the methods. The protocol was not available.
Other bias	Unclear risk	Not known if baseline characteristics were balanced across groups.

***Table 15**: Risk of bias assessment table for McCarty 2002 (165)*

PROGRESS 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As this was an open label continuation of previous trials, only the placebo groups were randomised. An interactive web response system was used for the randomisation process. Randomisation stratified according to demographics.
Allocation concealment (selection bias)	Low risk	Only placebo groups were randomised by used of an interactive web response system.
Blinding of participants and personnel (performance bias)	Low risk	Both participants and study staff were blinded to treatment. Medications were matched in both appearance and packaging.
Blinding of outcome assessment (detection bias)	Low risk	Both participants and outcome assessors were blinded to allocation.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for.
Selective reporting (reporting bias)	Low risk	All outcomes stated were then reported.
Other bias	Low risk	Baseline characteristics were balanced across groups.

***Table 16**: Risk of bias assessment table for PROGRESS 2017 (171)*

Ratjen 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive web response system used to randomise participants, who were stratified by weight and percent predicted FEV_1
Allocation concealment (selection bias)	Low risk	Randomisation from interactive web response system.
Blinding of participants and personnel (performance bias)	Low risk	Placebo tablets were matched to test intervention tablets.
Blinding of outcome assessment (detection bias)	Unclear risk	Does not say whether outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for.
Selective reporting (reporting bias)	High risk	Multiple outcomes were stated in methods but not reported in results.
Other bias	Unclear risk	Similar baseline characteristics in both groups.

***Table 17**: Risk of bias assessment table for Ratjen 2017 (168)*

Rubenstein 1998

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that randomisation & blinding were performed by an independent party but does not state how.
Allocation concealment (selection bias)	Unclear risk	States randomisation & blinding were performed by an independent party but does not state how.
Blinding of participants and personnel (performance bias)	Unclear risk	Study describes itself as double blind. It states that randomisation & blinding were performed by an independent party but does not state how.
Blinding of outcome assessment (detection bias)	Unclear risk	Study describes itself as double blind. It states that randomisation & blinding were performed by an independent party but does not state how.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for.
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods were all reported in results. Protocol was not available.
Other bias	Low risk	Baseline characteristics were balanced.

***Table 18**: Risk of bias assessment table for Rubenstein 1998 (166)*

Taylor-Cousar 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician made the randomisation code which was then used in an interactive web response system.
Allocation concealment (selection bias)	Low risk	Interactive web response system was used.
Blinding of participants and personnel (performance bias)	Low risk	Participants and study team were blinded. A matched placebo was used.
Blinding of outcome assessment (detection bias)	Low risk	Participants and study team were blinded. A matched placebo was used.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for. Despite a small number of them being excluded, they are still accounted for and it is unlikely to have introduced bias.
Selective reporting (reporting bias)	High risk	Multiple outcomes were stated in protocol but not reported in results.
Other bias	Low risk	Final paper produced with help of medical writers, paid for by the sponsor, it is not thought that this introduced bias.

***Table 19**: Risk of bias assessment table for Taylor-Cousar 2017 (169)*

TRAFFIC 2015

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by use of web response system. Stratified by demographics.
Allocation concealment (selection bias)	Low risk	Randomisation by use of web response system.
Blinding of participants and personnel (performance bias)	Low risk	Participants and study staff blinded throughout. Placebo was matched to test drug by appearance and packaging.
Blinding of outcome assessment (detection bias)	Low risk	Participants and study staff blinded throughout.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation have been accounted for.
Selective reporting (reporting bias)	High risk	Several outcomes stated on clinicaltrials.gov were not reported in the paper.
Other bias	Low risk	High adherence and compliance rates throughout trial.

***Table 20**: Risk of bias assessment table for TRAFFIC 2015 (170)*

TRANSPORT 2015

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by use of interactive web response system. Stratified by demographics.
Allocation concealment (selection bias)	Low risk	Randomisation by use of web response system.
Blinding of participants and personnel (performance bias)	Low risk	Participants and study staff blinded throughout. Placebo was matched to the test drug by appearance and packaging.
Blinding of outcome assessment (detection bias)	Low risk	Participants and study staff blinded throughout.
Incomplete outcome data (attrition bias)	Low risk	All participants who underwent randomisation were accounted for.
Selective reporting (reporting bias)	High risk	Outcomes stated on clinicaltrials.gov were not reported in the paper.
Other bias	Low risk	High adherence and compliance rates throughout trial.

***Table 21**: Risk of bias assessment table for TRANSPORT 2015: (170)*

Zeitlin 2002

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Describes itself as randomised but does not describe the methodology behind this.
Allocation concealment (selection bias)	Unclear risk	Does not state method for allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Study team were aware of allocation, also likely that participants could become aware of allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Not enough information given to describe how blinding of outcome assessors was maintained.
Incomplete outcome data (attrition bias)	Unclear risk	All participants completed study, but authors do not state if all participants were included in analysis.
Selective reporting (reporting bias)	High risk	Multiple outcomes stated in methods were not reported in results.
Other bias	Low risk	Baseline characteristics were balanced.

***Table 22**: Risk of bias assessment table for Zeitlin 2002*

Summary of findings tables for triple therapy combinations in Cochrane systematic review 2019.

VX-659-tezacaftor-ivacaftor

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Triple placebo or placebo-tezacaftor-ivacaftor	VX-659 plus tezacaftor plus ivacaftor or VX-561				
Survival Follow-up: 2 to 4 weeks	No deaths reported	No deaths reported	NA	129 (2 studies)	Low (1,2)	
Quality of life: total score Follow-up: NA	Outcome not reported				NA	
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: up to 4 weeks	See comment	Significant improvement seen in: F508del/MF 80 mg group, MD 10.00 (95% CI 0.29 to 19.71); F508del/F508del group (400mg), MD 18.10 (95% CI 10.85 to 25.35); and VX-561 group, MD: 20.3 (95% CI 7.1 to 33.6). No such significant differences were seen in the other dose groups	NA	117 (1 study)	Low (1,3)	Higher score indicates a better outcome. Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from week 2 and week 4.
FEV_1 (% predicted): relative change from baseline Follow-up: up to 4 weeks	See comment	Statistically significant improvements seen in FEV_1 % predicted relative change from baseline in all dose levels & genotypes compared to placebo.	NA	117 (1 study)	Low (1,3)	Data analysed via a MMRM. Results can averaged from week 2 and week 4
FEV_1 (% predicted): absolute change from baseline	One study found a statistically significant improvement in absolute change in FEV_1 % predicted at the dose of 120 mg twice daily versus		NA	12 (1 study)	Low (1,3)	A second study (n = 117) found a statistically

Follow-up: 2 weeks	placebo, MD 10.00 % predicted (95% CI 3.04 to 16.96).				significant improvement in the absolute change in FEV_1 (L) at all dose levels and genotypes when compared to placebo.
Adverse events Follow-up: 2 to 4 weeks	There was no significant difference in the number of participants experiencing at least 1 adverse event between the intervention and placebo at any dose or for any genotype. There was also no statistical difference versus placebo relating to the severity of adverse events across all doses and genotype groups.	NA	129 (2 studies)	Low (1,3)	Longer-term data in a larger number of participants will be very important for adverse event data.
Time to first pulmonary exacerbation Follow-up: NA	Outcome not reported			NA	1 study (n = 117) did report no difference in the number of courses of antibiotics required or the number of pulmonary exacerbations between groups at all dose levels and genotypes.
CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV_1: forced expiratory volume at 1 second; MD: mean difference; MF: minimal function; MMRM: mixed model for repeated measures; NA: not applicable.					
1. Downgraded once due to risk of bias: unclear methodological information reported regarding blinding of outcome assessors and potentially selective reporting of outcomes 2. Downgraded once due to imprecision: no data available and only measured in a small number of participants over a short timescale. 3: Downgraded once due to indirectness / lack of applicability: Data doesn't include children and those with more severe disease. Also short-term data only.					

***Table 23**: Summary of findings - Triple combination therapy (VX-659-tezacaftor-ivacaftor/VX-561)*

VX-445-tezacaftor-ivacaftor

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Triple placebo or placebo-tezacaftor-ivacaftor	VX-659 plus tezacaftor plus ivacaftor or VX-561				
Survival Follow-up: 4 weeks	No deaths reported	No deaths reported	NA	123 (1 study)	Low (1,2)	
Quality of life: total score Follow-up: NA	Outcome not reported				NA	
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: 4 weeks	A statistically significant improvement in the CFQ-R respiratory domain was observed versus placebo across all dose levels and both genotypes.		NA	123 (1 study)	Low (1,3)	A higher score indicates a better outcome.
FEV_1 (% predicted): relative change from baseline Follow-up: 4 weeks	A statistically significant improvement in FEV_1 relative change from baseline in favour of the intervention was observed versus placebo across all dose levels and genotypes.		NA	123 (1 study)	Low (1,3)	
FEV_1 (% predicted): absolute change from baseline Follow-up: NA	Outcome not reported		NA	NA	NA	1 study (n = 123) reported a statistically significant improvement in the absolute change from baseline in FEV_1 (L) favouring the intervention across all dose levels and genotypes

Adverse events Follow-up: 4 weeks	There was no significant difference in the number of participants experiencing at least 1 adverse event between the intervention and placebo at any dose or for any genotype. There was also no statistical difference versus placebo relating to the severity of adverse events across all doses and genotype groups.	NA	123 (1 study)	Low (1,3)	Longer-term data in a larger number of participants will be very important for adverse event data.
Time to first pulmonary exacerbation Follow-up: NA	Outcome not reported.			NA	1 study (n = 123) observed no difference in the number of courses of antibiotics required or the number of pulmonary exacerbations between groups all dose levels and genotypes.
CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; $FEV_{1:}$ forced expiratory volume at one second; MD: mean difference; MF: minimal function: NA: not applicable.					
1. Downgraded once due to risk of bias: unclear methodological information reported regarding blinding of outcome assessors and potentially selective reporting of outcomes. 2. Downgraded once due to imprecision: no data available and only measured in a small number of participants over a short timescale. 3: Downgraded once due to indirectness / lack of applicability: Data doesn't include children and those with more severe disease. Also short-term data only.					

***Table 24**: Summary of findings- Triple combination therapy (VX-445-tezacaftor-ivacaftor/VX-561)*

GRADE levels of evidence (as stated in the above tables):

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Trial	UK '91 Screening	Wisconsin '98 screening	Button '03	Doumi t '12	Stutman '02	Gibson '03	Wainwrigh t '11	Rosenfeld '12	Cohen '05	Costantini '01
Adequate sequence generation?										
Allocation concealment?										
Blinding? All outcomes										
Incomplete outcome data addressed? All outcomes										
Free of selective reporting?		Not in risk of bias table								
Free of other bias?										
Overall risk of bias										

Table 25: *Larger version of risk of bias assessment table for study of reported outcomes*

The James Lind Alliance's cystic fibrosis PSP's top 10 research priorities

1. Finding ways to simplify the burden of treatment which people with CF have.
2. Ways to improve relief of gastrointestinal issues such as abdominal pain, nausea, bloating.
3. Best treatment & when to start it for non-tuberculous mycobacterium infections in CF.
4. Identifying the best ways of preventing, delaying or slowing the progression of lung disease in the early life of those with CF.
5. Explore potential ways of preventing CF related diabetes.
6. Ways of motivating and supporting adherence to treatment.
7. Is it possible for exercise to replace chest physiotherapy?
8. Antibiotic regimes- what combinations and doses should be used during exacerbations and should they be rotated?
9. Ways to reduce problems associated with antibiotics such as resistance, adverse effects.
10. Look for the best way of eradicating Pseudomonas aeruginosa.

Poster for review of outcomes

Presented at European Cystic Fibrosis Conference, Liverpool 2019.

Clinical trials in pre-school children with cystic fibrosis; are we measuring the right outcomes?

Jared Murphy[1], Ian P Sinha[1,2], Alan R Smyth[3], Nikki Jahnke[4], Tracey Remmington[4], Kevin W Southern[1,2]

1: Department of Women's and Children's Health, University of Liverpool, 2: Alder Hey Children's Hospital, Liverpool; 3: Division of Child Health, Obstetrics and Gynaecology, University of Nottingham; 4: Cochrane Cystic Fibrosis & Genetic Disorders group, University of Liverpool.

Background

Conducting clinical trials in pre-school children with CF (pscwCF) is a challenge and there is no formal consensus on the best outcomes to measure and report in this age group.

Core outcome sets exist to provide guidance on the minimum standard required of clinical trials for which outcomes they should measure and report. Providing at least this minimum amount of appropriate information could have the effect of reducing heterogeneity of trials, allowing easier, and higher quality data synthesis for systematic review and decision making. The first step towards creating a core outcome set is to assess the current state of outcome reporting in pscwCF.

Aim: To record and characterise outcomes reported in trials of interventions for 0-5 year olds with CF.

Methods

We identified all Cochrane systematic reviews examining interventions for pscwCF. From these, we identified RCTs that exclusively enrolled pscwCF. We recorded and classified all outcomes mentioned in the protocol (where available), methods and results of each eligible systematic review and RCT into two theme sets; one set developed by the research team reflecting outcomes listed in the systematic reviews: Airway, Microbiology, Extra-thoracic disease, Patient/parent reported, Nutrition and Other; and the second set consistent with the Core Outcome Measures in Effectiveness Trials (COMET) initiative: Death, Physiological/clinical, Life impact, Resource use, Adverse events.

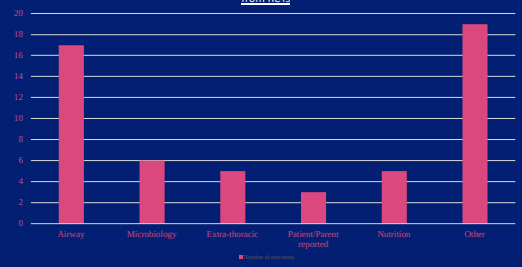
Example of different outcomes	Respective research team CF theme for this outcome	Respective COMET theme for this outcome
FEF 25-75	Airway	Physiological/clinical
Number of oesophageal reflux episodes	Extra-thoracic disease	Physiological/clinical
Quality of life	Patient/parent reported	Life impact
Anthropometric measure of nutrition/growth	Nutrition	Physiological/clinical
Number of exacerbations	Microbiology	Physiological/clinical
Duration of hospital stay	Other	Resource use

Table 1 – Examples of outcomes reported in included RCTs, and how they were classified according to both the CF research team's themes and the COMET initiative themes.

Results

We identified 29 systematic reviews of relevant interventions for pscwCF. Those reviews contained 295 trials, 10 were eligible for inclusion in this study. For 6/10 trials the risk of bias was high (unclear in 3, low in one).

Figure 1- Number of different outcomes, classified according to themes identified from RCTs

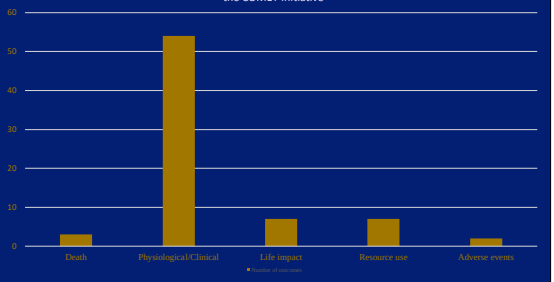


65 different outcomes were reported 127 different times.

The most common themes for the study team's theme set were 'Other' (n=19) and 'Airway' (n=17). The most common COMET theme was 'Physiological/clinical' (n=54).
The least commonly reported of the study team's themes was 'Patient/parent reported' (n=3). The most similar theme in the COMET set, 'Life impact', was reported 7 times.

See figures 1 and 2 for a breakdown of how many outcomes are reported under each theme.

Figure 2- Number of different outcomes, classified according to themes identified by the COMET Initiative



Discussion

Despite a wide search, only ten eligible trials were identified, six had significant quality issues (high risk of bias). This reflects the challenge of research in pscwCF; highlighted by the large number of outcomes measured. The Majority of outcomes identified were classified as surrogate biomarkers of short term physiological status, with FEV1 alone (a measure known to have little value in pre-school children) being reported in 5 different RCTs. There was a lack of pragmatic, longer term outcomes, more reflective of the lived experience of CF families. The pre-school years are vital for the future health of people with CF and the lack of comparative effectiveness research in pscwCF is disappointing.
Further, more comprehensive publications of this work will likely present the total number of outcomes reported across the protocols, methodologies and results of all included Cochrane systematic reviews and RCTs. This work paves the way for further work toward creation of a core outcome set. This will require engagement with multiple stakeholders such as patients, families, clinicians and commissioners, and is commonly performed by means of a Delphi study.

Conclusion

A clear core outcome set would be a useful step for facilitating high quality research in this age group.

E-poster slides for review of outcomes

Presented at European Cystic Fibrosis Conference, Liverpool 2019.

1.

UNIVERSITY OF LIVERPOOL

Alder Hey Children's NHS
NHS Foundation Trust

Clinical trials in pre-school children with cystic fibrosis; are we measuring the right outcomes?

Jared Murphy[1], Ian P Sinha[1,2], Alan R Smyth[3], Nikki Jahnke[4], Tracey Remmington[4], Kevin W Southern[1,2]

1: Department of Women's and Children's Health, University of Liverpool, 2: Alder Hey Children's Hospital, Liverpool; 3: Division of Child Health, Obstetrics and Gynaecology, University of Nottingham; 4: Cochrane Cystic Fibrosis & Genetic Disorders group, University of Liverpool.

Background

Conducting clinical trials in pre-school children with CF (pscwCF) is a challenge.
There is no formal consensus on the best outcomes to measure and report in this age group.
Core outcome sets provide guidance on the minimum standard required of clinical trials for which outcomes they should measure and report. Providing at least this minimum information could reduce heterogeneity, allowing easier, and higher quality data synthesis for systematic review and decision making.
The first step towards creating a core outcome set is to assess the current state of outcome reporting in pscwCF.

2.

Methods

1. We identified all Cochrane systematic reviews examining interventions for pscwCF.
2. From these, we identified RCTs that exclusively enrolled pscwCF.
3. We recorded and classified all outcomes mentioned in the protocol (where available), methods and results of each eligible systematic review and RCT into two theme sets; one set developed by the research team reflecting outcomes listed in the systematic reviews (table 1, below) and the second set consistent with the Core Outcome Measures in Effectiveness Trials (COMET) initiative (table 2, below):

Table 1: Cystic Fibrosis themes	Table 2: COMET themes
Airway	Death
Microbiology	Physiological/clinical
Extra-thoracic disease	Life impact
Patient/parent reported outcomes	Resource use
Nutrition	Adverse events
Other	

Example of different outcomes	Respective research team CF theme for this outcome	Respective COMET theme for this outcome
FEF 25-75	Airway	Physiological/clinical
Number of oesophageal reflux episodes	Extra-thoracic disease	Physiological/clinical
Quality of life	Patient/parent reported	Life impact
Anthropometric measure of nutrition/growth	Nutrition	Physiological/clinical
Number of exacerbations	Microbiology	Physiological/clinical
Duration of hospital stay	Other	Resource use

Table 3 – Examples of outcomes reported in included RCTs, and how they were classified according to both the CF research team's themes and the COMET initiative themes.

3.

Results

- We identified 29 systematic reviews of relevant interventions for pscwCF.
- Those reviews contained 295 trials, 10 were eligible for inclusion in this study.
- For 6/10 trials the risk of bias was high (unclear in 3, low in one).
- 65 different outcomes were reported 127 different times.
- The most common themes for the study team's theme set were 'Other' (n=19) and 'Airway' (n=17). The most common COMET theme was 'Physiological/clinical' (n=54).
- The least commonly reported of the study team's themes was 'Patient/parent reported' (n=3). The most similar theme in the COMET set, 'Life impact', was reported 7 times.

Figure 1- Number of different outcomes, classified according to CF themes identified from RCTs

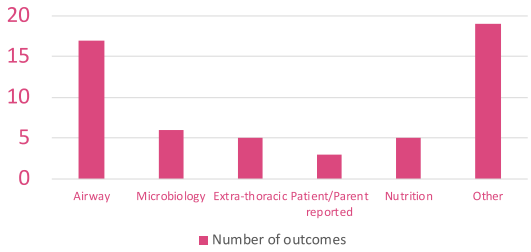
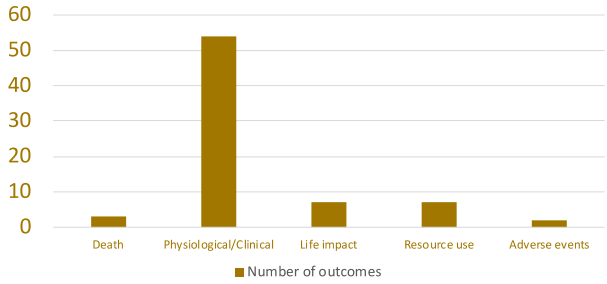


Figure 2- Number of different outcomes, classified according to themes identified by the COMET Initiative



4.

Discussion

- Despite a wide search, only ten eligible trials were identified, six had high risk of bias- reflecting the challenge of research in pre-school children with CF, which is further highlighted by the large number of different outcomes (n=65) measured in this small number of trials.
- The Majority of outcomes identified were classified as surrogate biomarkers of short term physiological status.
- There was a lack of pragmatic, longer term outcomes, more reflective of the lived experience of CF families.
- The pre-school years are vital for the future health of people with CF and the lack of comparative effectiveness research in pscwCF is disappointing.

Future work

- Further, more comprehensive publications of this work will likely present the total number of outcomes reported across the protocols, methodologies and results of all included Cochrane systematic reviews and RCTs.
- This work paves the way for further work toward creation of a core outcome set.
- This will require engagement with multiple stakeholders such as patients, families, clinicians and commissioners, and is commonly performed by means of a Delphi study.

Conclusion

- A clear core outcome set would be a useful step for facilitating high quality research in this age group.

Outcomes listed in systematic reviews

Protocol stage

Protocol								
Outcome	**Count**							
Indices of pulmonary function	28	(1 where pr	FEV0.5	2		CXR score	4	
LCI	3		FEV1	28	1 where pr	CT Score	2	
Rate of decline of FEV1 & FVC	1		FVC	28	1 where pr	Total	6	
radiology scores	5		FEF25-75%	12	1 where protocol unavailable			
radiological ventilation scanning	2		FEF75	1				
Clinical severity scores	2		RV	2				
Number of exacerbations	13		TLC	1				
Time to next exacerbation	3		RV/TLC	2				
Number of URT exacerbations	1		TLC	1				
Colonisation with any organism/new organi	9		FRC	2				
emergence of resistant organism	5		Exp reserve	1				
emergence of pseudomonas	6		LCI	3				
Time to next/chronic pseudomonas or other	3		plethysmo	1				
emergence of resistant pseudomonas	2		Thoracic ga	1				
Eradication of pseudomonas or other organi	2		PEFR	1				
resistance patterns	1		VC	1				
Markers of immune response to pseudomon	1		FEV1/VC	1				
Antibody levels to influenza A & B	1		Non-specifi	2				
Time to next resp infection	1		**Total**	90				
Nutritional status/growth/weight/body con	27							
nutritional intake	1			Colour	Theme			
eating behaviour	1				Airway			
Need for hospital admission	2				Extra thoracic disease			
Number of hospital admissions	8	1 where protocol unavailable			Patient/parent reported outcomes			
Number of hospital days	16	1 where protocol unavailable			Nutrition			
outpatient treatment/interactions	1				Microbiology			
Need for intensive care	1				Other			
Number of resp complications	1							
Need for additional antibiotics	6							
Number of days of additional antibiotics	10	1 where protocol unavailable						
Number of antibiotic courses	3							
Need for oxygen therapy	1							
Duration of oxygen therapy	1							
Occurrence of Diabetes								
Occurrence of liver complications	1							
Occurrence of respiratory complications	1							
mortality	11							
Survival/age at death	7							
Adverse events	25							
Adherence/drop out	7							
Quality of life	21							
Days unable to perform ADLs	1							
Symptoms/ symptom score	2							
Patient reported satisfaction to interventior	3							
time off work or school	1							
Oxidative stress markers	1							
inflammatory markers	3							
Hepatic enzyme levels	1							
USS- liver size	1							
USS- spleen size	1							
USS-portal vein velocity	1							
USS- presence of varices	1							
Hepatic scintigraphy- biliary excretion level	1							
Complications of portal hypertension	1							
need for liver transplant	1							
Exercise tolerance	6							
Airway mucus clearance	5							
Sputum characteristics	1							
oxygen sats	4							
cost	4							
change in bronchial hyperreactivity	1							
Gastroesophageal reflux appearance	1							
Gastroesophageal reflux worsening	1							
Symptoms of increased gastric acidity	1							
Complications of increased gastric acidity	1							
Bone health/vitamin D	1							
PTH levels	1							
Bowel symptoms	1							
Number of times vitamin deficiency is diagn	1							
measure of fat absorption	2							
Faecal fat excretion	2							
Vitamin E: total lipid ration	1							
Serum vit E levels	1							
Incidence of Vit E deficiency disorders	1							
Medication delivery time	1							
Time to next course of IV antibiotics	1							
Resp signs & symptoms	1							
Total	357							
Airway	102							
Extra-thoracic disease	16							
Patient/parent reported outcomes	28							
Nutrition	37							
Microbiology	71							
Other	103							
Total	357							

Methods stage

Methodology								
Outcome	Count	post hoc addition						
Indices of pulmonary function	8			FEV0.5	4		CXR score	4
LCI	4			FEV1	28		CT Score (u	1
Rate of decline of FEV1 & FVC	1			FVC	28		Brody CT sc	1
radiology scores	6			FEF25-75%	11			
radiological ventilation scanning	2			FEF75	1			
Clinical severity scores	3			RV	2			
Number of exacerbations	16			TLC	2			
Time to next exacerbation	5			RV/TLC	1			
Number of URT exacerbations	1			TLC	1			
Isolation of any organism/new organism	10	1		FRC	2			
emergence of resistant organism	5			Exp reserve	1			
emergence of pseudomonas	3			LCI	6			
Occurrence of/Time to next/chronic pseudor	5			plethysmo	1			
emergence of resistant pseudomonas	4			Thoracic ga	1			
Eradication of pseudomonas or other organis	2			PEFR	1			
resistance patterns	1			VC	1			
Markers of immune response to pseudomona	1			FEV1/VC	1			
Antibody levels to influenza A & B (serologica	1			Non-specifi	2			
Time to next resp infection								
Nutritional status/growth/weight/body com	25							
nutritional intake	1							
eating behaviour	1							
Need for hospital admission	3							
Number of hospital admissions	11							
Number of hospital days	17							
outpatient treatment/interactions	1							
Need for intensive care	1							
Number of resp complications	1							
Need for additional antibiotics	8							
Number of days of additional antibiotics	12							
Number of antibiotic courses	5							
Need for oxygen therapy	1							
Duration of oxygen therapy	1							
Occurrence of Diabetes	1							
Occurrence of liver complications	1							
Occurrence of respiratory complications	1							
mortality	11							
Survival/age at death	7							
Adverse events	28							
Adherence/drop out	6							
Quality of life	25							
Ability or otherwise to perform ADLs	2							
Symptoms/ symptom score	1							
Patient reported satisfaction to intervention	2							
time off work or school	1							
Oxidative stress markers	1							
inflammatory markers	4							
Hepatic enzyme levels	1							
USS- liver size	1							
USS- spleen size	1							
USS-portal vein velocity	1							
USS- presence of varices	1							
Hepatic scintigraphy- biliary excretion level	1							
Complications of portal hypertension	1							
need for liver transplant	1							
Exercise tolerance/activity levels	8							
Airway mucus clearance	4							
Sputum characteristics	3							
oxygen sats	4							
cost	6							
change in bronchial hyperreactivity	1							
Gastroesophageal reflux appearance	1							
Gastroesophageal reflux worsening	1							
Symptoms of increased gastric acidity	1							
Complications of increased gastric acidity	1							
Bone health/vitamin D	1							
PTH levels	1							
Bowel symptoms	1							
Number of times vitamin deficiency is diagno	1							
measure of fat absorption	2							
Faecal fat excretion	2							
Vitamin E: total lipid ration	1							
Serum vit E levels	1							
Incidence of Vit E deficiency disorders	1							
medication delivery time	1							
Cognitive function	1							
Plasma antioxidants	1							
plasma fatty acids	1							
Resp signs & symptoms	2							
Activity levels (post hoc)								
Time to next course of IV antibiotics	2							
Total								
Airway	106							
Extra-thoracic disease	17							
Patient/parent reported outcomes	31							
Nutrition	37							
Microbiology	85							
Other	120							
Total	396							

Results stage

Results							
Outcome	Count						
Indices of pulmonary function	27		FEV0.5	3		CXR score	3
LCI	7		FEV1	26		Chrispin-n	2
Rate of decline of FEV1 & FVC	1		FVC	25		CT score (n	2
radiology appearance/scores	6		FEF25-75%	7		Brody CT score	
radiological ventilation scanning	2		FEF75				
Clinical severity scores	5		RV	1			
Number of exacerbations	10		TLC				
Time to next exacerbation	5		RV/TLC				
Number of URT exacerbations	1		TLC	2			
Isolation of any organism/new organism/sp	11		FRC	1			
emergence of resistant organism	4		Exp reserve	1			
emergence of pseudomonas	5		LCI	6			
Occurrence of/Time to next/chronic pseud	5		plethysmo	1			
emergence of resistant pseudomonas	3		Thoracic gas volume				
Eradication of pseudomonas or other orgar	2		PEFR	1			
resistance patterns	1		Non-specifi	3			
Markers of immune response to pseudomo	1						
Antibody levels to influenza A & B (serologi	1						
Time to next resp infection							
Nutritional status/growth/weight/body co	23						
nutritional intake	1						
eating behaviour							
Need for hospital admission	6						
Number of hospital admissions	8						
Number of hospital days	14						
outpatient treatment/interactions	1						
Need for intensive care	1						
Number of resp complications	1						
Need for additional antibiotics	6						
Number of days of additional antibiotics	11						
Number of antibiotic courses	3						
Need for oxygen therapy	1						
Duration of oxygen therapy	1						
Occurrence of Diabetes	1						
Occurrence of liver complications	1						
Occurrence of respiratory complications	1						
mortality	11						
Survival/age at death	8						
Adverse events	28						
Adherence/drop out	5						
Quality of life	23						
Ability or otherwise to perform ADLs							
Symptom score							
Patient reported satisfaction to interventic	2						
time off work or school	1						
Oxidative stress markers	1						
inflammatory markers	3						
Hepatic enzyme levels	1						
USS- liver size	1						
USS- spleen size							
USS-portal vein velocity							
USS- presence of varices							
Hepatic scintigraphy- biliary excretion leve	1						
development of portal hypertension or co	1						
need for liver transplant	1						
Exercise tolerance/activity levels	8						
Airway mucus clearance	5						
Sputum characteristics	3						
oxygen sats	4						
cost	7						
change in bronchial hyperreactivity	1						
Gastroesophageal reflux appearance	1						
Gastroesophageal reflux worsening	1						
Symptoms of increased gastric acidity	1						
Complications of increased gastric acidity	1						
Bone health/vitamin D	1						
PTH levels	1						
Bowel symptoms	1						
Number of times vitamin deficiency is diag	1						
measure of fat absorption	2						
Faecal fat excretion	1						
Vitamin E: total lipid ration	1						
Serum vit E levels	1						
Incidence of Vit E deficiency disorders	1						
medication delivery time	1						
Cognitive function	1						
Plasma antioxidants	1						
plasma fatty acids	1						
Resp signs & symptoms							
Activity levels (post hoc)							
Time to next course of IV antibiotics	1						
Total							
Airway	88						
Extra-thoracic disease	14						
Patient/parent reported outcomes	26						
Nutrition	33						
Microbiology	73						
Other	121						
Total	355						

Outcomes listed in RCTs

Methods

Methodology	
Outcome	**Count**
Pulmonary function testing	4
Radiology findings/scores	5
Symptom/severity score	2
Quality of life	1
Parent reported symptoms	1
Nutritional status anthropometry/growth/weig	7
Nutritional biochemical markers (clotting, ferri	1
Dietary/calorie/protein/carbs/fat/vitamin intak	1
LFTs	1
fat soluble vitamins	2
fatty acids	2
fat absorption studies	1
pancreatic function	1
IRT level	2
immunological markers	1
mortality	1
Attendance at appointments	1
Virology results	0
Culture/bacteriology results (sputum & stool)	5
Acquisition of pseudomonas	3
Time to pseudomonas/pseudomonas free time	1
BAL bacteriology	2
Eradication of pseudomonas	1
Acquisition of other pathogens	1
Isolation of resistant bacteria	1
Use of antibiotics	1
Number of antibiotic courses	2
Duration of antibiotics	1
Drug concentration	1
Adverse events	5
Adherence/withdrawal	2
Number of exacerbations	3
Time to first/next exacerbation	1
Number of hospitalisations	3
Number of hospital days	2
URT symptoms	1
Wheeze	2
Cough	1
Number of reflux episodes	1
Duration of reflux episodes	1
Fractional reflux time	1
Oesophageal pH	1
Occurrence of reflux episode	1
Oxygen sats	3
Heart rate	1
Resp rate	1
Arousal state	1
Inflammatory indices	0
Changes in uses of pulmonary meds	1
Duration of steroid usage	1
Physical examination findings	2
Total	
Airway	15
Extra-Thoracic disease	6
Patient/parent reported outcomes	2
Nutrition	15
Microbiology	23
Other	36
Total	97

Non-specific PFT	2
FVC	2
FEV1	1
FEF	1
FRC	1
FEF75	1
FEV0.5	1
RV	1
TLC	1

Brasfield score	2
non-specific cxr	3
CF-CT score	1
Chrispin-normar	0

Colour	Theme
	Airway
	Extra thoracic disease
	Patient/parent reported outcomes
	Nutrition
	Microbiology
	Other

Results stage

Results							
Outcome	Count						
			FEV1/FVC	2		non-specific CXF	1
Pulmonary function testing	5		ppFEV1/FVC	1		Brasfield score	3
Radiology findings/scores	6		ppFEV1	1		Wisconsin CXR s	1
Symptom/severity score	4		ppFEF25-75	1		Chrispin-norma	1
Quality of life	1		Residual capacity:total lu	3		CF-CT score	
Parent reported symptoms	2		FVC	5			
Parent reported characteristics- apetite, bowel h	0		FEV1	5			
Parent reported number of infections	1		FEF25-75	6			
Nutritional status anthropometry/growth/weigl	10	One doesn'	FRC	3			
Nutritional biochemical markers (clotting, ferrit	2		FEV0.5	2			
Dietary/calorie/protein/carbs/fat/vitamin intak	1		FEF75	1			
LFTs	1		RVRTC	1			
fat soluble vitamins	1		ERV	1			
fatty acids			FEF75	1			
fat absorption studies							
pancreatic function	1						
IRT level							
immunological markers	0						
mortality	1						
Age at death	1						
Cause of death	1						
Attendance at appointments	1						
Virology results	1						
Culture/bacteriology results (sputum & stool)	1						
Acquisition of pseudomonas	2						
Number of pseudomonas acquisitions	1						
Time to pseudomonas/pseudomonas free time	2						
BAL bacteriology	2						
Eradication of pseudomonas	1						
Pseudomonas serology	1						
Acquisition of other pathogens	2						
Time to first/next infection (other)	1						
Isolation of resistant bacteria							
Use of antibiotics	2						
Use of chronic maintenance antibiotics	1						
Number of antibiotic courses	1						
Duration of antibiotics	5						
Drug concentration	1						
Adverse events	5						
Adherence/withdrawal	3						
Number of exacerbations	2						
Time to first/next exacerbation							
Number of hospitalisations	3						
Number of hospital days	4						
Reason for hospital admission	0						
URT symptoms	1						
Wheeze	1						
Cough	1						
Number of reflux episodes	2						
Duration of reflux episodes	1						
Fractional reflux time	1						
Oesophageal pH	1						
Occurrence of reflux episode							
Oxygen sats	6						
Heart rate	1						
Resp rate	1						
Arousal state	1						
Inflammatory indices	1						
Changes in uses of pulmonary meds							
Duration of steroid usage							
Physical examination findings	1						
Total			Number of different outcomes				
Airway	36		Airway	17			
Extra-Thoracic disease	6		Extra-Thoracic disease	5			
Patient/parent reported outcomes	4		Patient/parent reported o	3			
Nutrition	15		Nutrition	5			
Microbiology	26		Microbiology	16			
Other	40		Other	19			
Total	127		Total	65			