



UNIVERSITY OF
LIVERPOOL

**The impact of continuous glucose
monitoring on the management of
people with cystic fibrosis-related
diabetes**

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by Aileen Toner

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Table of Contents

Table of Contents	2
Abstract	5
Acknowledgements	7
List of tables	8
List of figures	9
List of abbreviations	10
Aims of this work	12
1. Introduction	13
1.1 Cystic Fibrosis	13
1.2 Diagnosis of CF	14
1.3 Cystic Fibrosis-related diabetes	14
1.3.1 The impact of CFRD on people with cystic fibrosis	15
1.3.2 Screening and Diagnosis of CFRD	18
1.3.3 Pathophysiology of CFRD	18
1.3.4 Monitoring and Management of CFRD	19
1.4 Diagnosis of CFRD	21
1.5 Continuous glucose monitoring	23
1.5.1 CGMS to diagnose CFRD	25
1.5.2 CGM to monitor CFRD	26
2. Evidence-based medicine and the systematic review	27
2.1 What are systematic reviews and meta-analyses?	27
2.1.1 Heterogeneity	30
2.2 Why perform a systematic review?	30
2.3 Limitations of a systematic review	31
2.4 The Cochrane Collaboration	32
3. Methodology for the CFRD Cochrane systematic review	34
3.1 Background	34

3.1.1 Description of the intervention.....	34
3.1.2 How the intervention might work.....	35
3.1.3 Why it is important to do this review	36
3.1.4 Objectives.....	36
3.2 Stakeholder engagement and patient involvement.....	36
3.3 Methods.....	38
3.3.1 Searching for studies.....	38
3.3.2 Assessing eligibility for inclusion.....	39
3.3.3 Outcomes recorded	41
3.3.4 Data Extraction.....	42
3.3.5 Risk of bias	43
3.3.6 Measures of treatment effect.....	45
3.3.7 Heterogeneity	46
3.3.8 Meta-analysis and sensitivity analysis.....	47
4. Results of the CFRD Cochrane systematic review	48
4.1 Context of the results	48
4.2 Results of the selection process.....	48
Identification	48
Screening	48
Eligibility	48
Included	48
4.2.1 Included studies	49
4.2.2 Ongoing studies.....	49
4.2.3 Excluded studies.....	50
4.3 Assessing risk of bias and the quality of evidence	54
4.3.1 The GRADE framework.....	56
4.4 Effects of interventions	57
4.5 Summary of results	57
4.6 Overall completeness and applicability of evidence	58

4.7 Potential biases in the review process.....	58
4.8 Agreements and disagreements with other studies or reviews	59
4.9 Creating a framework for future studies	59
5. Discussion.....	60
5.1 Summary of findings	60
5.1.1 Available evidence	62
5.2 Development of outcome measures for this review	64
5.3 Limitations	65
5.4 Implications for clinical practice	66
5.5 Implications for research.....	67
5.5.1 Discussion of future trial formats.....	68
5.5.2 Limitations when devising studies	70
6. Conclusion	72
References.....	73
Appendices.....	81
Blank summary of findings table for studies included in the Cochrane systematic review	81
Full search strategy	85
The James Lind Alliance’s cystic fibrosis PSP’s top 10 research priorities (2017).....	89

Abstract

Background

Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity found in people with cystic fibrosis (pwCF). CFRD is associated with increased adverse outcomes and burden of treatment in pwCF as well as reduced quality of life. People with CFRD (pwCFRD) must measure their blood glucose levels several times per day to monitor their diabetes and so that treatment can be tailored to individuals.

Continuous glucose monitoring systems (CGMS) are a relatively new technology that have been shown to be useful in *diagnosing* CFRD, but the impact of CGM on the monitoring and subsequent management of CFRD remains undetermined. This application of CGM has previously been approved in people with other forms of diabetes.

Method

For this work, engagement with stakeholders was undertaken to devise outcomes of interest that would make a meaningful impact on the lives and wellbeing of pwCFRD and those involved with their care. A protocol for an original Cochrane systematic review on the impact of CGM on pwCFRD was then created and the review itself was conducted. This included performing a comprehensive search of five major databases and assessing the eligibility of the results for inclusion in the study. A suggested framework for future research in this area was then created.

Results

Out of a total of 1768 studies, once duplicates were eliminated, there were found to be no completed RCT studies that appropriately fitted the protocol's criteria for inclusion in the review. The only study that did meet the criteria was a single RCT protocol registered at clinicaltrials.gov (NCT03939065) which had not yet been undertaken, and thus, presented no data to be analysed for the review at this time. However, once this trial is completed, it may be eligible for inclusion in an update of this review.

Discussion

There is currently no evidence to support the costly implementation of CGM to manage CFRD, although there are indications that CGMS are already being used in this context.

CFRD is becoming more prevalent because of a range of factors including the improved life expectancy of pwCF. The impact of CFRD on peoples' lives is of ever-growing importance and so it is now more pressing than ever to conduct research into ways to help alleviate both the treatment and disease burden for pwCFRD. Ensuring new technologies are properly evaluated will contribute to the provision of a growing and robust body of evidence which in turn will support the decision-making of policy makers, clinicians, and patients alike. As discussed, there is currently no data available on the impact of CGM on the management of pwCFRD. However, it is noted that the absence of evidence is not evidence of absence of effect. It is hoped that publication of this review will raise the profile of the question at hand and generate sufficient research to provide a route map to find the answers.

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I would also like to thank Nikki Jahnke, Tracey Remington and Natalie Hall, for their time, patience, and expertise from the very beginning. I am grateful for their round the clock advice which helped shape the creation of the Cochrane protocol and review, upon which this work is based.

I am grateful for the support I received from my co-authors; Dr Dilip Nazareth, Dr Freddy Frost, Paula Dyce and Anna McCloy, whose hard work and feedback helped propel this review and I look forward to continuing our work together in finalising the review for publication.

Lastly, I could not have undertaken this year without the unwavering support of my parents which, alongside the encouragement of my friends, family and loved ones, is always greatly appreciated. Thank you!

List of tables

Table 1: Categorising hypoglycaemia identified by CGMS (60).....	24
Table 2: Table of articles excluded at the full text stage.....	51
Table 3: Example of a summary table of risk of bias outcomes following assessment of studies included in a hypothetical Cochrane review.....	54
Table 4: Example of a hypothetical risk of bias assessment explanation table for “Study X”.....	56
Table 5: The four levels of evidence in the GRADE framework.....	56
Table 6: Possible interventions arms for a two-armed RCT investigating the use of CGM for CFRD.....	69
Table 7: Possible interventions arms for a three-armed RCT investigating the use of CGM for CFRD.....	70

List of figures

Figure 1: Methods of diagnosing CFRD (14, 28)	23
Figure 2: Abnormal CGM trace in a pwCFRD recently started on insulin therapy	25
Figure 3: A normal CGM trace	25
Figure 4: An example of a forest plot comparing relative change in % predicted FEV ₁ for azithromycin versus placebo. From 'Macrolide antibiotics for cystic fibrosis' by Kevin W Southern et al. 2004 (69)	29
Figure 5: A PRISMA (98) flow diagram detailing the stages at which different numbers of studies were excluded.	48

List of abbreviations

ADA	American Diabetes Association
ANZCTR	Australia and New Zealand Controlled Trials Register
BMI	Body Mass Index (kg/m ²)
CBG	Capillary blood glucose(s)
CENTRAL	The Cochrane Central Register of Controlled Trials
CF	Continuous glucose monitoring
CFGD group	(Cochrane) Cystic Fibrosis and Genetic Disorders group
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CF WISE	Cystic fibrosis withdrawal of inhaled steroids evaluation study
CGMS	Continuous glucose monitoring system(s)
CI(s)	Confidence Interval(s)
DKA	Diabetic ketoacidosis
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDAS	Healthcare Databases Advanced Search
HR	Hazard ratio(s)
JLA	James Lind Alliance
MDT	Multidisciplinary team
NGT	Normal glucose tolerance
NHS	National Health Service
NICE	National Institute for Clinical Excellence
OGTT	Oral glucose tolerance test(s)
OR	Odds ratio

PSP	Priority setting partnership(s)
pwCF	People (or person) with cystic fibrosis related diabetes
pwCFRD	People (or person) with cystic fibrosis related diabetes
QDS	Four times per day
QOL	Quality of life
RCT(s)	Randomised control trial(s)
SAP therapy	Sensor augmented pump therapy
SR(s)	Systematic review(s)
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
USA	United States of America
(WHO) ICTRP	(The World Health Organisation's) International Clinical Trials Registry Platform

Aims of this work

- Engage with stakeholders to identify which outcome measures are most important to people with cystic fibrosis related diabetes.
- Formulate, for publication, a protocol for an original Cochrane systematic review; *'Continuous glucose monitoring systems for people with cystic fibrosis related diabetes.'*
- Perform and produce a Cochrane review for publication from said protocol.
- Establish a framework for future trials to improve the evidence base on the impact of CGM on the management of pwCFRD.

1. Introduction

In preparation for this year of study, I spent time with the cystic fibrosis (CF) team at Alder Hey Children's Hospital in Liverpool. I attended several CF clinics and had the opportunity to engage with young people with CF, and their families, to understand more about their experiences. This enabled me to identify that CF related diabetes presented considerable difficulties for a small, but significant, number of them. During these clinics, I had the opportunity to observe continuous glucose monitoring systems (CGMS) in situ. This led to deciding to explore how these novel devices could be used to make a difference to pwCF and their carers. This involved using and developing my existing research skills and experience of academic collaborative research, specifically, systematic reviews. From this initial engagement with pwCF, about what matters most to them about their diabetes and treatment, I further decided to use stakeholder engagement to devise outcomes for the review reflecting what patients themselves considered to be the most important factors rather than strictly clinical parameters of disease progress or status.

1.1 Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal-recessive genetic condition which affects multiple systems, primarily the lungs; leading to the main cause of mortality in people with the condition being respiratory failure (1). Multiple other bodily systems are also affected, most notably the digestive and reproductive systems. It is associated with Cystic Fibrosis Related Diabetes (CFRD); the most common extrapulmonary co-morbidity in people with CF (pwCF) (2).

CF is one of the most common life-shortening disorders; patients with CF survive to a median age of approximately 47 years according to the Cystic Fibrosis Trust, with one in twenty-five people of northern-European descent estimated to carry the gene (3, 4). Globally, 70,000 people have CF and 1 in 2500 new-borns in the UK are estimated to be affected, leading it to be a particularly prevalent disease that carries significant morbidity and mortality.

Pathological variation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, located on chromosome 7, causes production of malfunctioning or non-functioning CFTR transmembrane proteins leading to the impaired transport of salts (especially

chlorides) across epithelial cell membranes within the body. The pancreas is one of the organs most frequently damaged by this pathology; progressive fibrosis and fatty infiltration resulting in insufficient pancreatic endocrine and exocrine activity and the most common comorbidity of CF being CFRD (5). CFRD will be discussed in depth later in this chapter.

This imbalance in ion transport also leads to the inappropriate osmotic sequestration of water which manifests primarily through the production of excessively thick mucus at epithelial sites including the airways, reproductive organs, gastrointestinal system, hepatobiliary tract, and the pancreatic ducts. The thickened mucus secreted at these sites results in a variety of complications including recurrent and/or chronic bacterial colonisation leading to enduring inflammation which leads to fibrosis. It is this progressive fibro-cystic change in affected organs which results in deterioration of function over time, ultimately leading to significant morbidity and mortality in patients with CF.

The most recent (2018) data report from the UK Cystic Fibrosis Registry (sponsored and managed by the Cystic Fibrosis Trust) estimates the median survival of pwCF born in 2018 to be around 44 years old for females, and 51 for males (1). The report states that while there has been a decreasing rate of mortality amongst people with CF over the last 30 years, the primary cause of death in this group remains to be cardiorespiratory failure, as in previous years (1).

1.2 Diagnosis of CF

There are several methods of identifying when a person has CF. It is commonly identified shortly after birth through a newborn bloodspot screening test, implemented in the UK since 2007. In some cases, CF is diagnosed antenatally through amniocentesis or chorionic villus sampling; identification of a meconium ileus on an ultrasound scan may raise suspicion of the presence of CF. If CF is otherwise clinically suspected, for example in a child with faltering growth or recurrent respiratory infections, this can then be confirmed through a positive sweat test or gene testing revealing two disease-causing variants.

1.3 Cystic Fibrosis-related diabetes

Cystic fibrosis-related diabetes (CFRD) is a particularly common comorbidity found in pwCF. As the life expectancy of pwCF improves, tackling CFRD presents a growing challenge to

patients and clinicians alike. This is due in part to the fact that prevalence of CFRD is associated with increasing age, with around 2% of children, 20% of adolescents and 50% of adults thought to have the condition (2). The median age of onset is 20 years of age (6-8). Females are also thought to be at higher risk of developing CFRD and are likely to do so sooner than males (6, 9). In addition to age and sex, other risk factors for CFRD include a family history of type 2 diabetes mellitus, pancreatic insufficiency, CF-related liver disease and possessing a more severe genotype (10), which unfortunately includes the most common variant; $\Delta F508$ (F508del) (11).

Compared to pwCF who don't have diabetes, people with CFRD (pwCFRD) experience significantly increased morbidity and mortality (by almost 6-fold (12)) with a substantial decline in lung function and nutritional status often being the first manifestation of the disease; beginning two to six years before a formal CFRD diagnosis by oral glucose tolerance test (OGTT) has been made (7, 11, 13-15). Thus, CFRD presents unique challenges for clinicians, patients, and families alike, highlighting the vast need for accurate and timely diagnosis and effective management.

Compared to other forms of diabetes, pwCFRD have an insulin deficiency with a delayed and diminished bolus response to carbohydrate loads, with sparing of basal insulin secretion. This contributes to normal fasting glucose and postprandial hyperglycaemia being a common occurrence in pwCFRD (16). The inappropriately delayed insulin response to a glucose load often leads to hypoglycaemia in pwCF who are not diabetic and can be observed on OGTT (17). The characteristic pattern of glycaemia in pwCFRD consists of glucose levels being lowest prior to breakfast, with peaks after each meal, and highest following the final meal of the day (16). A visual depiction of this pattern is available in section 1.5.

1.3.1 The impact of CFRD on people with cystic fibrosis

1.3.1.1 Survival

As mentioned, CFRD is associated with significantly increased mortality, especially in females, compared to pwCF with normal glucose tolerance (NGT).

1.3.1.2 Lungs

Given that mortality in CF is often from progressive lung failure (1), perhaps the most important impact of CFRD on the morbidity and mortality of pwCF is the hastened decline in

lung function (forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁)) associated with insulin deficiency and hyperglycaemia.

Inflammation of the airway epithelium, such as that seen in pwCF, increases epithelial permeability to glucose. When coupled with hyperglycaemia, which heightens the glucose gradient across the epithelial barrier, this can lead to an increase in the glucose concentration of the airway surface liquid that lines the lung (18). In some pwCFRD, a CGM reading of 8mmol/l and above has been linked to the detection of glucose in the airway surface liquid. The same study showed an increase in the growth of organisms such as *pseudomonas aeruginosa* and *staphylococcus aureus* when airway surface liquid glucose concentration rose to just 0.5-4mmol/l, likely contributing to pwCFRD experiencing an increase in infection and decrease in lung function (16). This could help explain why having CFRD is also linked to developing reduced gas diffusion, increased effort of breathing and more lung stiffness and structural disease than pwCF who have NGT (16, 19, 20). It is therefore likely that this pathology both contributes to and is exacerbated by an increased number of pulmonary exacerbations, inflammation of the airways, and bacterial colonisation as discussed (21, 22).

1.3.1.3 Nutritional Status

For pwCF, having a higher BMI is associated with reduced bone loss, maintaining the immune system and having better lung function (23). This makes maintaining an individual's target BMI a major goal in managing the treatment of pwCF; around 22kg/m² for females and 23kg/m² for males according to the Cystic Fibrosis Foundation (24). Good nutrition is a key part of managing CF, even in the absence of diabetes, and is achieved through nutritious high calorie diets devised and tailored by CF specialist dieticians within the multidisciplinary team (MDT). People with CF have higher resting calorie turnover and metabolic rate than the average person due to increased energy expenditure because of factors such as acute or chronic infection and increased work of breathing.

Additionally, around 85% of pwCF are born with or develop pancreatic insufficiency before their first birthday, a hallmark of CF (25). This is when the exocrine function of the pancreas is below the level needed to allow a person to maintain their health without intervention. This means that most pwCF cannot adequately absorb carbohydrates, protein and, importantly, fats. Fats contain vital fat-soluble vitamins (A, D, E and K) and a high calorie load

meaning that pwCF are routinely given vitamin supplements and pancreatic enzyme replacement therapy to help meet their nutrition goals (26). This combination of malabsorption and high energy turnover leaves pwCF vulnerable to the substantial decline in nutritional status seen in CFRD.

This is likely, in part, due to the characteristic insulinopenia; promoting a catabolic state which makes it more difficult for pwCFRD to maintain their lean body mass (11). This trait is also seen in people with T1DM but is likely exacerbated in CFRD by the additional pathology discussed above.

1.3.1.4 Diabetic Ketoacidosis

Diabetic ketoacidosis is a serious complication of insulin-dependent forms of diabetes. Fortunately, it is relatively uncommon in CFRD as unlike in T1D, pwCFRD do not develop an absolute insulin deficiency; instead, retaining some basal insulin secretion (27).

1.3.1.5 Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state is rarely seen in CFRD (28).

1.3.1.6 Macrovascular complications

Macrovascular complications seen in other forms of diabetes are uncommon in pwCFRD.

1.3.1.7 Microvascular complications

Significant long-term complications such as retinopathy, nephropathy and neuropathy seen in CFRD are comparable to those observed in individuals with type 1 diabetes mellitus (29). While the prevalence of diabetic retinopathy and nephropathy in pwCFRD are lower than that seen in people with type 1 or type 2 diabetes, retinopathy still occurs in 10-23% of pwCFRD (29-31). PwCFRD are more likely than their non-diabetic counterparts to have autonomic neuropathy and may exacerbate the gastrointestinal dysfunction already experienced by many pwCF (30).

These complications are dependent on disease duration as well as glycaemic control (11) thus, the American Diabetes Association (ADA) (28) recommends that CF patients known to have had CFRD for at least 5 years should be routinely tested for microvascular disease (30).

1.3.1.8 Quality of life

All the above complications have the potential to increase the burden of treatment and to adversely impact the quality of life experienced by pwCF. Having CFRD in itself can significantly reduce the health-related quality of life experienced by pwCF, and the addition of insulin therapy to their already intensive treatment regime significantly contributes to the overall treatment burden they experience (32).

1.3.2 Screening and Diagnosis of CFRD

Early diagnosis and optimisation of glycaemic control has been shown to vastly improve lung function, nutritional status and overall survival rates (2, 28, 33, 34), making regular screening from a young age a vital part of routine care of pwCF.

Due to the high incidence of CFRD Amongst CF patients, the consensus between the Cystic Fibrosis Foundation (35) and the American Diabetes Association (28), as well as current NICE guidelines (14) state that people with CF should be tested for CFRD annually from the age of ten, especially as CFRD can begin to cause damage before a person starts experiencing symptoms (14, 36). Additional or earlier investigation is warranted if a patient is receiving long-term steroid treatment or experiencing unexplained weight loss, excessive fatigue, a drop in Forced Expiratory Volume in one second (FEV₁) or increased frequency of pulmonary exacerbations despite receiving optimised CF treatment. PwCFRD can also experience polydipsia and polyuria as symptoms.

Several screening tests have been used for CFRD: most commonly, the oral glucose tolerance testing (OGTT), serial glucose monitoring by capillary blood glucose (CBG) and continuous glucose monitoring (CGM) (14, 28). The appropriateness and utility of these methods for the diagnosis of CFRD are discussed in chapter 1.4.

1.3.3 Pathophysiology of CFRD

CFRD does share some clinical characteristics with both Type 1 and Type 2 diabetes (T1DM and T2DM, respectively) but is recognised as its own distinct condition (28). While both T1DM and CFRD are associated with a decline in insulin secretion, the autoimmune

pathogenesis noted in the former is not seen in CFRD; levels of antibodies in pwCF with NGT are the same as in pwCFRD (37).

The pathophysiology of CFRD is multifaceted and still not fully understood. The overarching theme is that gradual destruction of the pancreas in CFRD leads to pancreatic insufficiency and insulinopenia, complicated by end-organ resistance to insulin (14). In CFRD, the typical viscous mucus produced in CF causes pancreatic duct obstruction; triggering inflammation and ischaemic changes, atrophy of the pancreatic islets, and progressive fibrosis and fatty infiltration within the endocrine pancreas (38-40). Destruction of the insulin-producing β -cells causes insulin deficiency, reducing the ability of the pancreas to respond to post-prandial increases in blood glucose leading to progressive glucose dysregulation and damaging hyperglycaemia.

The CF-causing CFTR gene variants may also play a direct role in the development of CFRD as functional CFTR has been shown to be crucial for normal beta cell function (37).

1.3.4 Monitoring and Management of CFRD

Subcutaneous insulin is the mainstay of treatment while oral diabetes medications such as metformin and sulfonylureas are not usually recommended in CFRD (14, 28, 35).

The ADA recommends that people with CFRD, who take insulin, should track their glycaemic control using the traditional CBG method at least three times a day (28). This data, obtained and noted by pwCFRD or their carers, is then collated by clinicians to evaluate an individual's overall glycaemic trends, allowing an individual's CFRD treatment to be tailored to their specific individual needs. CGM is a newer form of monitoring glucose levels in diabetes (41) and investigating the utility of this in the context of CFRD forms the basis for this work. Rigorous monitoring of glucose levels facilitates the specific adjustments of elements of CFRD management including titration of insulin dosage and frequency, nutritional factors to improve clinical outcomes for pwCFRD. Thus, CFRD treatment is multidimensional and best confronted via an MDT approach.

1.3.4.1 Insulin therapy

Insulin is an anabolic hormone which stabilises and improves glycaemic control as well as lung function and reverses chronic weight loss decline experienced by pwCFRD prior to

diagnosis and treatment (33, 42). As in T1DM, insulin is the primary treatment for CFRD (28), but the associated targets and regimens differ from those used to tackle other forms of diabetes.

For pwCFRD, multiple daily injections or insulin pump therapy is often required to achieve adequate reduction in hyperglycaemia. Because pwCF still produce some insulin, these doses tend to be at lower quantities than those used in T1DM in order to safely counteract CFRD insulinopenia while avoiding inducing hypoglycaemia (43).

The long-term benefit of optimising glycaemic control with insulin encompasses not only a delay in decline of lung function by 34 months on average (44), but also a reduction in microvascular complications (28).

PwCF may have an increased insulin requirement during pregnancy, periods of taking corticosteroids, receiving enteral or intravenous feeds or during pulmonary exacerbations (35). A higher frequency of glucose testing is also usually necessary during these events.

1.3.4.2 Diet and exercise

The earlier described specially balanced diet followed by pwCF should not be altered if they are diagnosed with CFRD (28). Instead carbohydrates should be monitored and insulin adjusted accordingly in order to optimise glycaemic control (28).

Exercise is an important part of the health and wellbeing of the general population but conveys particular benefit to pwCF and pwCFRD in potentially helping maintain lung function and improve airway clearance (45). Exercise can reduce anxiety and depression for pwCFRD (46) and may also help reduce systemic inflammation and improve insulin sensitivity (47, 48). To maximise these benefits, pwCFRD are recommended to do at least 150 minutes of moderate intensity aerobic exercise per week (28).

1.3.4.3 CFTR potentiator and corrector therapy

There is no clear consensus on the effectiveness of CFTR gene-therapy modulators, such as Ivacaftor, in aiding the prevention and/or treatment of CFRD (40, 43, 49-51). In recent years it has been suggested that modulators may have a favourable effect on incidence of CFRD or

insulin secretion (40, 43, 49), but there is still no conclusive evidence, necessitating further research in this area.

1.3.4.4 Complications of CFRD management

Hypoglycaemia can be a serious and potentially life-threatening risk associated with injectable insulin regimens, but may be less common and severe in CFRD than in other forms of diabetes (52). This less severe hypoglycaemia can often be treated by the individual themselves, with glucose tablets for example. Some pwCF who are not on insulin therapy can spontaneously enter this low-level hypoglycaemic state, likely due to a combination of malabsorption, increased calorie turnover and dysregulated or delayed insulin secretion (11).

1.3.4.5 Impact on treatment burden

PwCF dedicate a substantial amount of time and effort to multiple intensive treatment therapies, averaging 150 minutes per day (53), not including attending regular outpatient appointments or spending time in hospital as an inpatient during exacerbations. This gives an idea of the significant treatment burden experienced by pwCF prior to a diagnosis of CFRD and the additional time and effort required to adequately monitor and manage glucose control that this brings. Mitigating the additional risks to health that CFRD poses involves adherence to an even more complex and rigorous treatment plan. As such it is important to investigate ways to reduce or simplify the significantly increased treatment burden experienced by pwCFRD compared to non-diabetic pwCF and to the general population (32).

1.4 Diagnosis of CFRD

CFRD should be diagnosed during a stable period of baseline health as acute illness or use of continuous enteral nutrition can cause fluctuating hyperglycaemia that may resolve when these stressors are overcome; this was previously termed 'intermittent-CFRD' (54).

However, in patients with an acute illness who sustain fasting blood glucose or 2-hour post-prandial plasma glucose levels above the 'normal' level (as detailed below) for over 48 hours, a diagnosis of CFRD may be made (28).

As mentioned, the most used diagnostic tests for CFRD include serial CBGs, OGTT and CGM. Routine CBG tests including serial random glucose readings above 11 mmol or fasting blood glucose (≥ 7.0 mmol/L) can be diagnostic of diabetes in pwCF (28).

While HbA1c could in theory diagnose CFRD, the sensitivity of HbA1c as a screening/diagnostic test is controversial since it may remain within the normal range even while damage is occurring from hyperglycaemia, this is not a widely used diagnostic parameter for diabetes in pwCF (11).

Although OGTTs are a relatively cheap method of screening for CFRD, there are several potential issues with the test. They can be time consuming and labour-intensive with multiple uncomfortable finger-sticks required over the course of one session. The values of an OGTT test indicating normal and abnormal glucose tolerance (NGT < 7.8 , IGT $\geq 7.8 - < 11.1$ and diabetes ≥ 11.1 mmol/L at 120-minutes) are drawn from a non-CF diabetic population who are thus geno-typically different. These existing diagnostic criteria for diabetes were based on the WHO criteria and the risk of developing micro-vascular complications in T2DM (55) rather than CF specific outcome. There is evidence that the 120-minute value fails to discriminate between healthy controls and those with CFRD (56). As the OGTT also has poor sensitivity and specificity in diagnosing CFRD (57), the applicability of the test in this context could be contested. For these reasons, it has been suggested that the diagnostic limits of this test in a CFRD context should instead be guided by the 'pulmonopathy' that occurs at very low level hyperglycaemia in pwCF (57). To mitigate the poor sensitivity and specificity of OGTTs in the diagnosis of CFRD, NICE guidelines recommend that an abnormal test be followed up with dynamic testing, such as serial CBGs or CGM for confirmation (14).

Performing an OGTT to diagnose CFRD in medically stable pwCF is currently recommended by the European Cystic Fibrosis Trust (35), the UK CF Trust (58) and ADA (28). NICE have recently updated their advice to include CGM as a valid diagnostic tool alternative to OGTT, demonstrating how it is becoming an increasingly more commonly used option (14, 59).

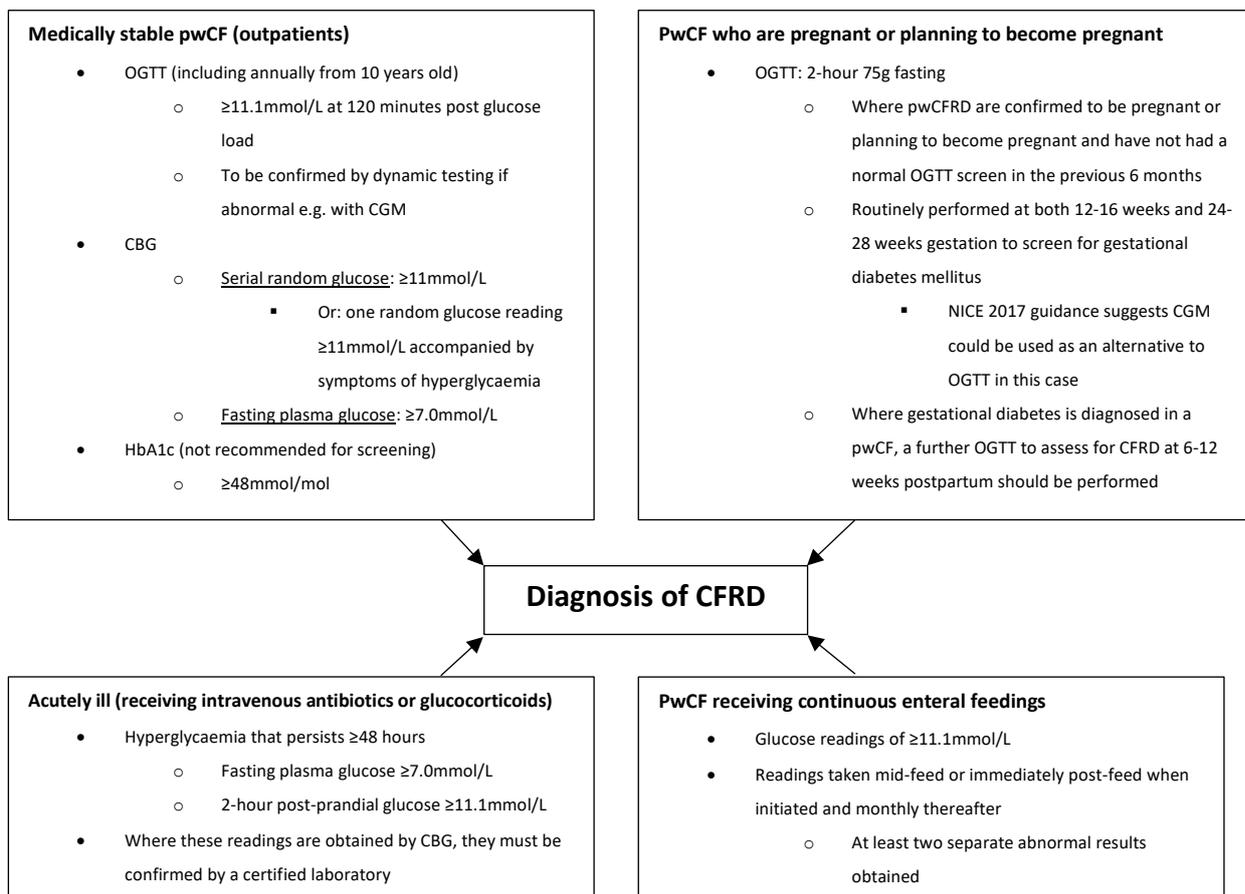


Figure 1: Methods of diagnosing CFRD (14, 28)

1.5 Continuous glucose monitoring

Continuous glucose monitoring systems (CGMS) are a relatively recent development and offer a less invasive alternative to CBG and work by transmitting blood glucose values, calculated from actual interstitial fluid glucose concentrations, measured by a subcutaneous sensor, to a display device or smart phone. Thus, unlike CBG, CGM reflects an individual's glucose trends rather than absolute plasma glucose levels (11). Because of the lesser accuracy of CGMS readings in the lower range, these values need to be cautiously interpreted. The International Consensus on Use of Continuous Glucose Monitoring have suggested the following ranges of CGMS data values are used to categorise hypoglycaemia severity (60):

Category of hypoglycaemia	Presentation	Indication
Level 1	3.9-3.0mmol/L (with or without symptoms)	<ul style="list-style-type: none"> At risk of impending hypoglycaemia Reduce time spent at this level to reduce

		risk of further hypoglycaemia
Level 2	3.0 mmol/L (with or without symptoms)	<ul style="list-style-type: none"> • Clinically significant hypoglycaemia • Immediate attention required • Given more weight in clinical studies than Level 1
Level 3	Severe hypoglycaemia (no specific glucose value)	<ul style="list-style-type: none"> • Cognitive impairment requiring external assistance for recovery

Table 1: Categorising hypoglycaemia identified by CGMS (60).

The sensor is inserted into the subcutaneous tissue of the individual's arm or lower abdomen by the individual or their carer and is then left in-situ for at least 72 hours or up to 10 days at a time. This provides semi-continuous 24-hour information, from glucose readings taken every five minutes, regarding glycaemic changes and trends through day and night, accumulating substantially more data than intermittent CBG monitoring.

For people using some older models of CGMS, it is sometimes recommended that they perform CBG at least once every 12 hours to calibrate the device. Some newer devices no longer require this input (61). A diary is kept tracking events with the potential to trigger significant glycaemic fluctuations such as: dietary intake, exercise (especially if vigorous), the consumption of sugary drinks, and administration of hyper/hypoglycaemic drugs, though this is not always necessary. This data can then be analysed and reconciled with glycaemic variability.

Below is an example of part of a CGM trace from a young person with CFRD who has recently started on insulin:

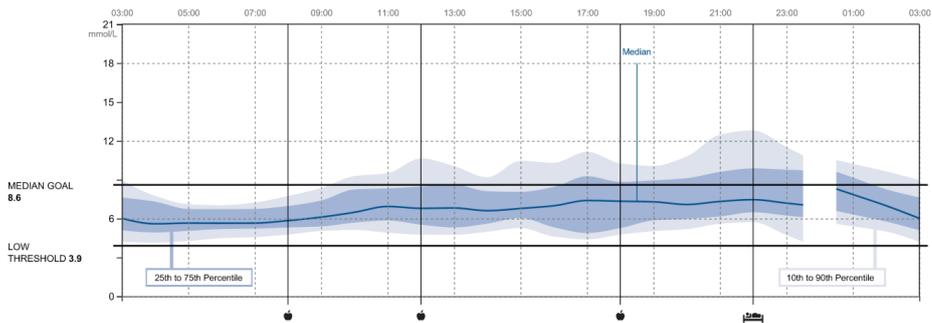


Figure 2: Abnormal CGM trace in a pwCFRD recently started on insulin therapy

Although the ‘median’ trace stays within the wearer’s target range, the upper range of their glucose profile across the weeks of CGM data indicates that they have still spent time in the hyperglycaemic range. Where the apple icons are situated below the trace marks when the wearer has had a meal, the typical postprandial hyperglycaemia experienced by pwCFRD is illustrated by delayed peaks in glucose after each of these, of increasing amplitude throughout the day. There is little or no indication that this person has experienced hypoglycaemia during this CGM trace as the lower limit of the normal glycaemic range has not been crossed.

For comparison, a normal CGM trace might look like this:

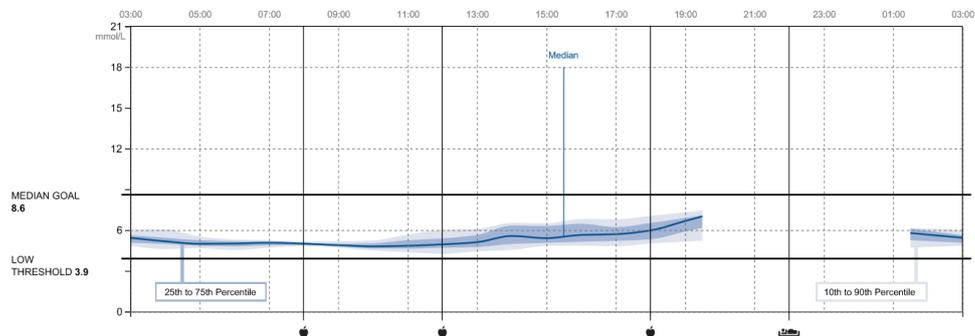


Figure 3: A normal CGM trace

In this trace, even across the several weeks that the CGM was recording glucose data, the wearer has had a gradual increase in glucose throughout the waking day, but never strays outside of their normal glucose range.

1.5.1 CGMS to diagnose CFRD

While CGMS were developed for monitoring glucose control in those with T1DM, these systems have recently emerged as a useful validated tool to diagnose CFRD (14, 62, 63). Because CGM collects data across a period of several days, it is likely a reliable way to

detect hyperglycaemia due to the variable nature of glucose dysregulation (14), and this is increasingly reflected in its use in clinical practice and inclusion in some major diagnostic guidelines (14). Other guidelines remain unchanged, citing that further work is needed to illustrate the effect of diagnosis through CGM on long term outcomes before it can be fully endorsed (59, 63).

1.5.2 CGM to monitor CFRD

CGM has been recommended as a form of glucose screening by the most recent NICE CFRD guidance (14). There are two main types of CGMS equipment and analysis: real-time versus retrospective data presentation.

‘Unblinded’ or real-time CGMS provide information to guide diet, exercise, and insulin therapy as an alternative or supplement to CBG, potentially reducing the discomfort and inconvenience of otherwise more frequent finger sticks. Some ‘true’ real-time CGM models integrate alerts for glucose levels above or below a pre-set threshold allowing immediate remediation of significant glycaemic fluctuations, whereas others require the user to scan the CGMS to obtain a glucose reading (intermittently scanned CGM).

‘Blinded’ or retrospective CGMSs similarly allow more detailed data trends to be observed than CBG but do not allow for immediate modification of glucose-altering factors in the way that real-time CGMS do as glucose levels are not displayed in real-time. These devices are worn for a period of time and the resulting data is considered by clinicians and patients together to assess overall glycaemic trends (62). However, when used in conjunction with diabetes management education and insulin dose adjustment, blinded CGM has been shown to aid the monitoring and management of other forms of diabetes, but not CFRD (62).

CGMS has been validated as a tool to both diagnose CFRD and proposed as a strategy to better manage CFRD than traditional means; potentially conveying benefits to patients’ weight and lung function as discussed (64). However, the impact of CGMS-guided insulin regimens on the lives of people with cystic fibrosis related diabetes remains unclear (65). Thus, the focus of this dissertation aims to address the question; “What is the evidence that CGM-lead treatment modification improves outcomes for pwCF diagnosed with CFRD?”

2. Evidence-based medicine and the systematic review

The world of medicine is complex and ever-changing. With novel healthcare treatments and advancements in therapeutic technologies emerging all the time, there is a need for the availability of up-to-date data evaluating the benefits and harms these interventions can bring, as well as identifying what the most appropriate therapies are within different clinical contexts. Practicing evidence-based medicine integrates clinical expertise with the best available external evidence (66), ensuring that informed decisions can be made in the best interests of a person's health and wellbeing.

However, with an ever-expanding wealth of such literature, often with inconsistencies across the final conclusions presented, systematic reviews (SRs) can offer a critical appraisal and summary of a large body of primary research to ascertain the overall answer to a specific question to assist individuals in their decision making. SRs of randomised controlled trials (RCTs) with meta-analysis represent the top tier in the hierarchy of evidence (67); summarising all the best available research to provide reliable estimates about the effects of an intervention, or demonstrate where a lack of knowledge on a subject exists and thus highlighting where future research should be directed.

2.1 What are systematic reviews and meta-analyses?

Undertaking a SR is a method of stringently identifying, critically appraising and collating all the available evidence across different studies to answer a pre-defined question in a methodical and reproducible way. To help reduce bias and ensure reliable conclusions are drawn, SRs are constructed around several defining features (68).

An explicitly recorded methodology is a key foundation for any SR and should be determined before the initiation of data collection; it should be watertight enough that peers may replicate the process, exactly as the original researcher performed it.

The literature search process should be systematic, ensuring all appropriate sources are explored to identify all studies relevant to the review question. The objectives of the SR, as well as the criteria by which studies will be excluded or determined eligible for inclusion, must be defined 'a priori' and should be stated clearly. The processes of assessing validity of

included studies as well as then extracting, synthesising, and reporting the data collected must be performed in a methodical fashion.

Meta-analysis is a method of statistically comparing and integrating the effect estimates and confidence intervals (CIs) from studies included in the review that are sufficiently like one another. It is often performed as part of the data analysis of an SR to draw conclusions about the total body of research. Meta-analyses can illustrate whether there is an overall benefit from the new intervention in comparison with a control i.e. usual care or placebo and whether this difference is a truly significant one or a reflection of the effect of random chance.

This illustration can be quite literal in the form of a forest plot, summarising key data from multiple studies into a single diagram to facilitate visual comparison of the range of treatment effects estimated in the literature. In a forest plot, the horizontal x axis represents the extent to which a study's results favour the intervention or the control, in a scale appropriate for the statistic being displayed such as an odds ratio or relative risk where a 'relative' statistic is concerned, versus absolute values scaled in absolute risk reduction or standardised mean difference. For relative values, at (1.0) on the x axis lies the vertical y axis; representing the line of null effect where there is no difference in outcome regardless of exposure to either intervention. Alternatively, for absolute values, the line of no effect intersects the x axis at (0.0).

Each study included in a forest plot is represented by a block, the position of which indicates a point estimate of its results, whereas the size of the block signifies the weight assigned to that study in the meta-analysis based on factors such as the number of participants involved. A horizontal line extends through each block, the width of which indicates the CIs for each study concerned; a wider line indicates a less reliable a study's findings are likely to be. If outcome being measured is desirable, such as improved lung function, results that sit to the right of the line of no effect indicate that exposure to the intervention of interest positively affected that outcome, compared to the control group. If the outcome being measured is undesirable, results to the left of the line indicate that the intervention of interest was more beneficial than the intervention to which those in the control group were exposed.

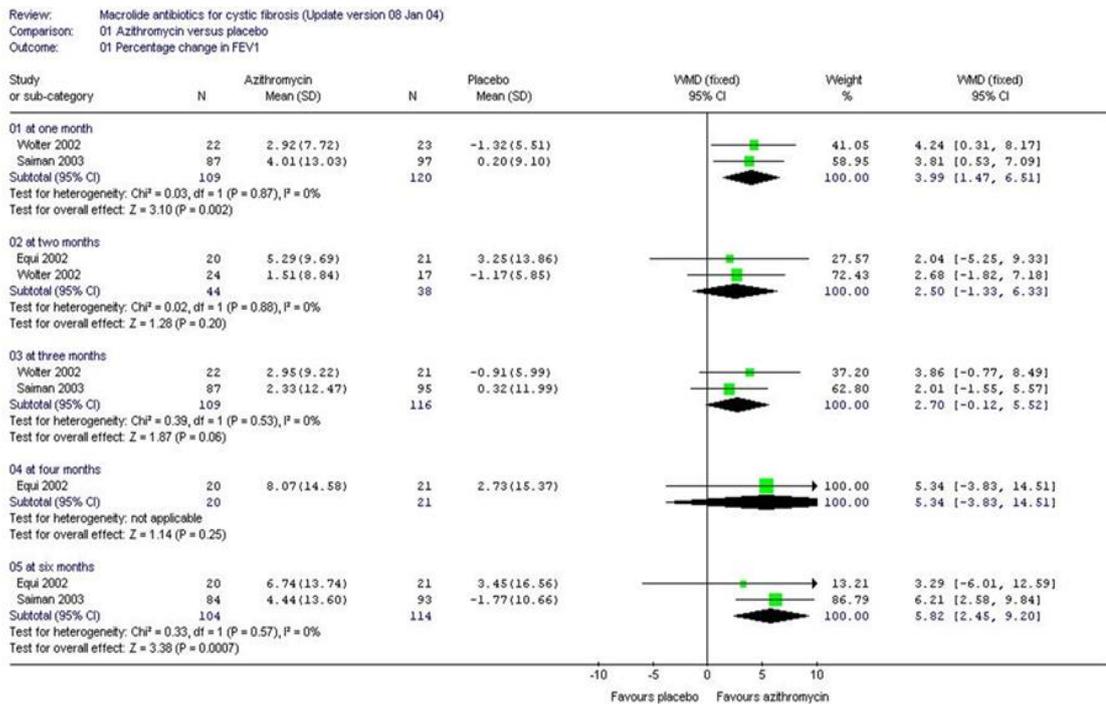


Figure 4: An example of a forest plot comparing relative change in % predicted FEV₁ for azithromycin versus placebo. From 'Macrolide antibiotics for cystic fibrosis' by Kevin W Southern et al. 2004 (69)

The diamond at the bottom of a forest plot is a combined average of all the studies in the graph and functions in a similar way to the blocks, with its width indicating the spread of the results between 95% CIs; the range of values in which we can be 95% certain that the true treatment effect lies. For this reason, smaller diamonds are an indication of greater confidence in the true effect. Diamonds can be interpreted from the diagram similarly to the results of individual studies as detailed above, however if any part of a diamond lies across the line of null effect, it indicates that the results are not statistically significant and so the intervention of interest does not make a meaningful difference to the outcome measured compared to the control group.

Studies that are investigating the same intervention and are recording similar outcomes should theoretically produce similar results. By visually representing the degree to which the results of studies overlap, or fail to do so, forest plots can give an indication of the presence of heterogeneity. Random variation can account for some differences between findings, but where overlap of studies on a forest plot is minimal, heterogeneity should be investigated and its potential effect on overall conclusions examined (68). Alternatively, where there is a significant amount of overlap in the same direction, the lack of variation of results can

indicate that they are more likely to demonstrate an accurate estimate of the true effect, a reflection of homogeneity.

2.1.1 Heterogeneity

Heterogeneity is the term used to describe causes of variation between the results of studies and can mainly be categorised as; clinical, methodological, or statistical heterogeneity.

- Clinical heterogeneity can be defined as the normal variation between the characteristics of participants in different studies such as age or severity of disease. It also accounts for diversity in certain features of the interventions studied such as method of delivery or dosage.
- Methodological heterogeneity refers to the fact that different study designs can yield different results e.g. a cluster-randomised trial vs. a cross-over trial. It can also arise from studies differing in how they record and interpret outcomes such as time points at which measurements will be taken, or studies with differing levels of risk of bias being inappropriately combined.
- Statistical heterogeneity can be caused by clinical heterogeneity and/or methodological heterogeneity and represents the random variation that occurs due between results of studies when they are measuring potentially similar but less-than identical effects. Excess variation can indicate that the effects studied may have been too significantly different to appropriately combine in a meta-analysis. Statistical heterogeneity is thus the type usually referred to when meta-analyses or systematic reviews discuss 'heterogeneity'.

2.2 Why perform a systematic review?

There are many advantages to SRs providing a comprehensive overview of the available literature on a specific topic, often supported by data synthesised through meta-analyses. They condense what can be an overwhelming number of studies, likely of varying quality and validity, into an accessible quality-assessed summary to aid evidence-based decision-making and save the time of those seeking reliable answers to the same question.

As a part of this process, SRs can help determine when sufficient investigative evidence has been collected to adequately resolve a research question, thereby reducing the need for further studies in that area, saving time and resources. When a clinical question has been satisfactorily answered, the SR can establish relevant implications for clinical practice and influence clinical guidelines, thus supporting the practice of evidence-based medicine.

Conversely, SRs can highlight where there is a lack of evidence on a topic, when few or no RCTs are found to be eligible for inclusion in an analysis, sometimes known as an 'empty review'. These empty reviews can still play an important role in medical research as in highlighting gaps in the knowledge base, they can provide a direct starting point upon which future clinical trials can be based. This has often been the case in Cochrane SRs about CF. (70) The Cochrane Cystic Fibrosis and Genetic Disorders (CFGD) group have collated a list of published empty SRs and the resulting major ongoing RCTs and completed RCTs that have led to changes in practice (71). One such example is a Cochrane SR entitled "inhaled corticosteroids for cystic fibrosis" (72) which prompted the CF WISE trial (73) run by Balfour-Lynn et al. which demonstrated the safety of stopping inhaled corticosteroids for some pwCF, reducing drug burden, side-effects and reducing costs.

Because RCTs are the gold standard for primary research into the effectiveness of an intervention (74), it follows that SRs of RCTs and the data they produce are considered as being better than other study designs in the hierarchy of evidence collection and can be viewed as a lens through which other studies can be collated and critically appraised (67). SRs can explore and resolve inconsistencies in results to give insight into what the true treatment effect is. For example, through meta-analysis, the process of weighting studies provides a clearer depiction of the precision of individual studies which can help readers to weigh up conflicting findings.

2.3 Limitations of a systematic review

The rigid methodological approach of SRs means that it is unlikely that all variations in circumstances, such as those present in day to day clinical practice, can be fully taken into consideration. SRs aim to answer a specific question, therefore if someone seeking information on a similar but unidentical topic, e.g. the same drug but in elderly patients, the evidence from the SR is indirect. This emphasises the need for clinical judgement to be integrated with evidence to form appropriate evidence-based medical decisions.

Where the literature base of individual studies investigated by the SR is biased, the SR itself will be biased (75) but by aiming to access unpublished literature, this bias may be mitigated to an extent. Where heterogeneity in findings is observed, it is important that the sources of this are investigated as this may reduce confidence in the effect estimates produced and undermine the credibility of the review.

Accurate quality assessment on the validity and risk of bias of studies can be challenging, particularly as methodology and data can poorly described in the literature. Cochrane authors are encouraged to contact the authors of included studies where data is missing in order to mitigate this, though it has been recognised in a Cochrane methodological review that efforts may not always be successful, particularly where older studies are concerned (76).

2.4 The Cochrane Collaboration

The Cochrane Collaboration is an independent, not-for-profit group that regularly produces and updates comprehensive systematic reviews from thousands of members across 130 countries for the last 25 years. These reviews support and inform evidence-based decision-making about healthcare issues (77). The organisation was founded in 1993 in the name of British epidemiologist Archie Cochrane, considered by some to be the ‘father of evidence-based medicine’ (78).

Dr Cochrane advocated for the inclusion of scientific evidence to guide medical practice within the NHS both in terms of treatment effectiveness and in appropriate allocation of resources (78). He advocated for and highlighted the importance of RCTs as an important source of evidence to substantiate the use of medical interventions, believing it to be more reliable than that from other sources (77).

The Cochrane Collaboration has formulated a stringent process, adherence to which allows high-quality SRs to be produced and this process is denoted in full in the ‘*Cochrane Handbook for Systematic Reviews of Interventions*’ (68). Demanding a reproducible protocol to be devised before a literature search can be carried out, alongside their rigorous editorial and peer-review processes, minimises the risk of bias affecting the SRs and ensures the results produced are reliable and credible (68). Consequently, Cochrane reviews are

regarded as the international quality benchmark for evidence regarding health care effectiveness (77).

3. Methodology for the CFRD Cochrane systematic review

3.1 Background

CGM has been validated as a novel tool to diagnose and manage CFRD earlier and more effectively than through traditional means (64), but the impact of CGMS-guided insulin regimes on the lives of people with cystic fibrosis related diabetes remains undetermined (59). A previous Cochrane review “Continuous glucose monitoring systems for type 1 diabetes mellitus” (79) evaluated the same health technology in patients with T1DM which has since been used to inform 6 clinical guidelines (80-85) on the appropriateness of CGM use in this context. As described, CFRD has similarities to T1DM, however it is still fundamentally a separate condition with unique features and so the data from this review cannot be directly extrapolated to inform the use of CGM in pwCFRD.

This work represents an original systematic review designed to investigate the impact, or lack thereof, of using continuous glucose monitoring systems to monitor glycaemia in CFRD. In particular, it was designed to evaluate whether modification of a person’s insulin regime (dosage, frequency, type of insulin administered etc.) guided by CGMS-collected data could affect the clinical outcomes and quality of life experienced by pwCFRD differently than traditional therapy i.e. insulin treatment guided by CBG.

3.1.1 Description of the intervention

CGMSs have been around since the late 1990s / early 2000s (86), with new and improved models being released by different brands semi-regularly since. Primarily used in non-CF diabetes, CGM has been validated as being comparable in CFRD (65, 87).

The devices record interstitial fluid glucose levels up to 288 times per 24 hours for at least three to five days, accumulating substantially more data than intermittent CBG monitoring. From this we can build a much more detailed picture of an individual’s glycaemic variability across the day and at night to help patients and clinicians make decisions about how to best tackle hyperglycaemia.

As detailed earlier in this thesis, CGMS have two major subgroups: real-time versus retrospective data presentation. Real-time or ‘flash’ CGMS readings can be viewed instantly, or the complete data set can also be downloaded to view retrospectively. On the other

hand, with retrospective CGMS, glycaemic data cannot be viewed immediately but can be downloaded to be analysed retrospectively. Both types were considered under the CGMS umbrella as a single intervention for the purposes of this review.

3.1.2 How the intervention might work

PwCFRD who take insulin are usually advised to perform and record CBG measurements a minimum of 3 times a day, with extra measurements also being necessary when experiencing symptoms of hypoglycaemia or before exercising.

CGM is a more recently developed and detailed form of glucose monitoring, sometimes used by people with T1DM (88), and investigating the utility of this in the context of monitoring CFRD forms the basis for this work. The data collected through these methods can be used by clinicians to titrate the doses, frequency of administration or type of insulin a pwCFRD takes to tackle hyperglycaemia and avoid hypoglycaemic events to improve outcomes (11). In theory, the maximal data sets produced by CGM could facilitate more precise changes to optimise treatment regimens since they may pick up glycaemic excursions that may be missed by the glycaemic snapshots taken with CBG monitoring.

The instant information available to pwCFRD using real-time or flash CGMSs, as an alternative or supplement to CBG, could help them tailor their diet, exercise, and insulin therapy more accurately. It could also offer an educational opportunity in terms of being able to visualise how different triggers affect their blood sugar levels and may reduce the discomfort and inconvenience of otherwise more frequent finger sticks. With both types of CGMSs, the wealth of data on an individual's insulin needs and responsiveness can be downloaded to be analysed by clinicians retrospectively.

UpToDate, an American advanced clinical decision support tool, has suggested that CGM can also be beneficial for pwCFRD who are not responding to standard therapy as well as expected, i.e. poor weight gain despite initiation of insulin therapy (11).

In theory, if the rigorous monitoring of glycaemic changes provided by CGM can help prevent or reduce hyperglycaemia in pwCFRD through facilitating more precise adjustments to therapy elements, particularly the insulin regime, this could improve key outcomes in pwCFRD including lung function and weight gain.

3.1.3 Why it is important to do this review

This review seeks to establish the impact of novel CGMS-guided insulin therapy (insulin regimen modification in response to CGMS excursion data) on the lives people with CFRD in comparison to insulin therapy guided by other forms of glucose data collection.

People with CF are a group of individuals with a high burden of treatment which increases with age, therefore trying to find ways of streamlining treatment to reduce this where possible is an important area to investigate (89, 90). As such, it is important to establish the impact of CGMS-led insulin tailoring on aspects of health and life that people with CFRD themselves consider to be particularly important, as depicted in the outcomes for this review. Implementing use of CGMS equipment is currently costly (14) even though this price is falling (91), and so it is not currently available everywhere. This further highlights the importance of making evidence available to stakeholders and funding bodies regarding the effectiveness of this health technology (14).

The topic “continuous glucose monitoring systems for monitoring CF-related diabetes” was previously listed as a priority review title by the Cochrane Cystic Fibrosis and Genetic Disorders group in March 2019 (92), highlighting the need for a review of evidence based research on the topic. The list has since been updated to reflect the title having been addressed by this review.

3.1.4 Objectives

To evaluate the impact of continuous glucose monitoring-guided insulin regimens, both positive and negative, on the lives of people with cystic fibrosis related diabetes (pwCFRD) according to outcomes considered important by pwCFRD.

3.2 Stakeholder engagement and patient involvement

For the purpose of cultivating a set of outcomes that would make meaningful difference to the lives of pwCFRD and their families, it was decided that stakeholder engagement would be undertaken, in the form of a semi-structured interview, to ascertain which outcomes were of most importance to those that would be affected by the results.

The stakeholders that were consulted for this review encompassed a variety of clinicians including CFRD specialist Advanced Nurse Practitioners and respiratory and CF specialist consultant and trainee physicians as well as ten individuals with CFRD and their families. This work was commenced in three clinical areas across two hospital sites to ensure that a variety of patients and clinicians were involved in the consultation process. These sites included a paediatric CFRD-specific CF clinic in Alder Hey Children's Hospital as well as both an adult CFRD outpatient clinic and an adult CF inpatient ward in Broadgreen Heart and Chest Hospital.

This variation in stakeholder recruitment environment meant that the pwCFRD also varied in both age and degree of disease severity, it was hoped that this could give a broader outlook on issues that matter to pwCFRD at different points in their lives. The selection of pwCFRD who were interviewed was based on who attended clinic or was on the ward on the day that the interviewer was present, who were also happy to partake in the discussion. A simple interview template of open questions was formulated beforehand, to guide the meetings, that was based on the combined clinical experiences of the review authors with the aim of exploring which aspects of their treatment mattered the most to pwCFRD.

Key themes highlighted through discussions with clinical staff largely revolved around the importance of preserving and improving lung function first and foremost, as well as other clinical parameters including maintaining in-range blood glucose values and the prevention of long term CFRD-related adverse outcomes. The discussions held with pwCFRD and their families carried a similar message but focussed on more wholistic aspects of the experience of patients. This raised key issues such as the amount of time pwCFRD were absent from school or work due to health-related issues, the additional burden of treatment that comes with the diagnosis of diabetes and how well an individual felt able to manage their condition and treatments independently. Maintaining their BMI and preventing weightloss was mentioned by every pwCFRD that was interviewed, viewed as their own indicator of how well they were doing with their condition, i.e. patients linked maintenance of body mass with better lung function, a lower rate of respiratory infections and being an indicator that their diabetes was under control. The frequency of this concern amongst pwCFRD clearly illustrates the importance of weight and BMI as a particularly meaningful outcome to them and their families.

The subsequent discussion of these aspects of patient experience furthered the authors' interest in the impact of CGM on the overall quality of life experienced by pwCFRD and contributed to this being prioritised as a primary outcome. The engagement process helped inform the decisions of authors in establishing and appropriately ordering subsequent outcomes for the Cochrane review, to improve the relevance of this review to consumers, as well as to inform ourselves as researchers.

3.3 Methods

3.3.1 Searching for studies

Ideally, the Cystic Fibrosis Trials Register search would be conducted by the Cochrane CFGD's Information Specialist. However, due to the time constraints of the MPhil and delays caused by the COVID-19 pandemic, this search was undertaken by author, AT. Relevant studies were sought using the terms: cystic fibrosis-related diabetes [CFRD] and impaired glucose tolerance [IGT], in accordance with the protocol. The Cystic Fibrosis Trials Register is an amalgamation of all clinical trials to date that concern CF; the register is maintained by the Cochrane CFGD group who regularly update it with studies found during frequent electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase. Trials added to the register are also identified through regular hand-searching of Pediatric Pulmonology and the Journal of Cystic Fibrosis and unpublished work is also sought from the abstract books of several key cystic fibrosis conferences for addition to the collection.

Additionally, the protocol stipulated that we intended to search the following databases and trial registries for relevant literature:

- Embase Healthcare Databases Advanced Search (HDAS) (1974 to present); (<https://hdas.nice.org.uk/>);
- Web of Science Core Collection (1900 to present);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);

- Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch).

The bibliographies of included studies and relevant systematic reviews would be examined for further references to applicable trials to ensure that no studies eligible for inclusion would be overlooked. Our search strategies were cultivated by the team of authors with input from the Cochrane CFGD information specialist to maximise the scope of the search and obtain all relevant trials. Details of our full search strategies can be found in the appendices.

Unfortunately, the unprecedented events surrounding the advent of the COVID-19 pandemic from March 2020 meant that access to the WHO ICTRP became restricted to staff within the WHO. This occurred during the initial data collection phase of the Cochrane review, mandating that this database was omitted for the purposes of this thesis due to time constraints. Despite this, every effort will be made to incorporate search results from the ICTRP into the final version of the systematic review before submitting it for publication.

3.3.2 Assessing eligibility for inclusion

Two review authors; AT and AM; independently applied the predetermined selection criteria to identify potential studies to be included for review, in line with the standards set out by Cochrane (68). A new data collation spreadsheet was created by AT to aid the screening of papers and for ease of comparison between the decisions made by AT and AM. The inclusion criteria we used for this process are to be peer reviewed and then published via the protocol in the Cochrane database to help minimise bias and to enhance the transparency of the research (93). The criteria considered the following aspects:

- Appropriate study design- All randomised controlled comparisons were included. Studies with a cross-over design, even with a washout period between intervention arms, were not eligible for inclusion due to the potential long-term impact of each of the interventions and thus potential to compromise the outcomes of the second intervention.

- Relevant participants - We included pwCF of any age who also had a diagnosis of CFRD as determined through the benchmarks discussed in Chapter One. There were no specific exclusion criteria for pwCFRD*.
- Relevant interventions - We were looking at the effects of insulin regimens led by CGMS data (including real-time or retrospective data, or both) as compared to insulin regimens guided by other means of glycaemic data collection. This included but was not limited to insulin regime modification in response to CBG monitoring by finger stick. Types of CGMS and comparators were eligible for inclusion regardless of the associated insulin dosage, frequency, or mode of delivery.
- Relevant outcomes - The outcomes of particular interest to the study are explored in the section below, however, if a study was identified as being relevant to the research question but did not report on the outcomes listed, this would not have warranted exclusion from the review and so it would still have been evaluated as part of this piece of work.

Using these parameters, the resulting titles and abstracts of these articles were initially screened, followed by analysis of the full text of studies determined to have the potential to meet the inclusion criteria. Where information needed to determine eligibility for inclusion was missing, or when only an abstract of an otherwise potentially eligible study was obtainable, we contacted the investigators (Stackhouse (94) and Jackson (95)) to attempt to retrieve the necessary data to clarify the inclusion status of the relevant papers. We aimed to resolve differences in opinion on inclusion through discussion where possible, or through referral to a third author for consensus when necessary.

*Where relevant studies containing mixed-participant samples would be identified (e.g. people with type 1 diabetes and people with CFRD included), the full review group would discuss on a case by case basis whether the studies should be included. If the consensus were that any such study should be included in the review, the relevant authors would be contacted to try and obtain the relevant specific subgroup data on the

CFRD patients for inclusion in the review. Where authors were unable or unwilling to provide the relevant data, these studies would not be included in any meta-analysis.

3.3.3 Outcomes recorded

To determine the following outcomes, previous papers related to the topic were reviewed and stakeholder engagement was undertaken as previously described. The outcome measures of interest did not form part of the specific criteria inclusion criteria for studies in this review.

Primary outcomes

1. Quality of life (QoL) (measured by a validated disease specific tool e.g. CFQ-QOL(96))
2. Treatment-related adverse outcomes (e.g. hypoglycaemia (defined as ≤ 3.8 mmol/L), contact dermatitis etc)

Secondary outcomes

1. Lung function
 - a) FEV₁ % predicted (change from baseline or absolute post-treatment values)
 - b) FEV₁ L (change from baseline or absolute post-treatment values)
 - c) change in lung function as measured by another valid parameter
2. Nutritional parameters
 - a) weight (kg or percentile)
 - b) body mass index (BMI) percentile
3. CFRD-related adverse outcomes (e.g. diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state, microvascular disease and hypertension, diabetic nephropathy, retinopathy and neuropathy, mortality)
4. Proportion of time within a normal blood sugar profile ($*\geq 7.8$ mmol/l $\geq 4.5\%$ of time < 70 – 54 mg/dL (3.9–3.0 mmol/L))
5. Burden of treatment
6. Self-efficacy** (as measured using a standardised scale e.g. General Self Efficacy Scale (97))
7. Time off school or work (self-reported or otherwise documented)

* 'Normal' range can vary between individuals

** Self-efficacy for the purposes of the review was defined as the extent to which an individual could (or felt confident in their ability to) manage the monitoring and treatment of their medical condition independent from their carer/parent or medical staff etc.

3.3.4 Data Extraction

Data extraction forms based on those provided by the Cochrane editorial team were customised by AT to aid independent data extraction by the authors. This would help present the data for synthesis in a more structured, organised manner.

Where differences in opinion occurred on the suitability of a study or its risk of bias, these would be resolved through discussion where possible, or through referral to a third author (DN) for consensus if necessary.

Included studies would be analysed and the following information extracted and collated into the data extraction form for each:

- Administrative information including first author, year of publication, country, language.
- Study participants including number of included participants in each group and their baseline characteristics such as age and sex, as well as the diagnostic criteria used and the regions from which participants were recruited.
- Study characteristics including design of study; recruitment and sampling procedures, inclusion and exclusion criteria, duration of follow up, outcome measures.
- Details of intervention techniques used for collection of the glucose level data and the corresponding insulin-dosage modification strategies. The integrity of interventions applied is also important to note; the degree to which interventions were implemented as planned e.g. how many days/hours of usable CGM data were collected.
- Data to address the primary and secondary outcome measures as prespecified in the protocol and the measurement tool used to assess these and the time points at which these were followed up.

These outcome data would be reported within several timeframe groups to account for variation in length of follow-up between studies:

1. up to two weeks
2. over two weeks and up to one month
3. over one month and up to three months
4. over three months and up to six months
5. over six months and up to one year
6. annually thereafter

Authors of studies including a subset of relevant data or missing data would be contacted for further information so that all available published or unpublished data on from included studies are included in the systematic review.

3.3.5 Risk of bias

Two review authors; AT and AM, would independently assess the risk of bias of studies to be included for review. The Cochrane Collaboration's tool for assessing risk of bias (98) would be used to inform the screening of articles and to categorise them into several domains as either: low risk of bias, high risk of bias or unclear risk of bias. Differences in opinion would be resolved through discussion where possible, or through referral to a third author for consensus where necessary.

The domains that are used to assess for risk of bias within studies are guided by those recommended in Cochrane's risk of bias tool (99) and handbook (100):

- Selection bias: evaluating the procedure used to generate the allocation sequence and whether the resulting groups would be sufficiently comparable.
- Concealing allocation: Identifying and gauging the effectiveness of the method used to conceal allocation sequence and whether this would adequately prevent participants and/or study personnel from foreseeing the distribution of interventions before or during the trial period.

- Performance bias: examining what methods were used in blinding both the participant and study personnel from learning of any one intervention allocation, and whether these measures were reported to be effective.
- Detection bias: assessing how the study personnel collecting outcome data were prevented from learning which patient was allocated which intervention, and whether these measures were reported to be effective.
- Attrition bias: appraising the amount or nature of incompleteness of outcome data, e.g. due to factors such as participant drop-out and whether this is adequately reported and explained by researchers. Participant drop-out discrepancies may be picked up by comparing the number of participants who received any given intervention against the total number of participants initially randomised.
- Reporting bias: determining the extent to which all outcomes of interest declared before the study began were subsequently measured and reported, and where reporting appears selective, whether researchers adequately and transparently detail reasons for this.
- Other bias: any other issues deemed by the authors to increase a study's risk of bias.

The results of are then input to a “risk of bias” assessment tool within the Cochrane Collaboration’s Review Manager software (101).

3.3.5.1 Publication Bias

When a study produces negative results, this may influence researchers to decide not to proceed with publishing the trial (102). This can result in publication bias where the amount of published literature shows disproportionately positive results when compared to the actual overall wealth of evidence that has been collected, because these represent the most studies to go to publication. The implications for this in a systematic review are that results can be skewed positively compared to the truth, leading to the possible

inaccuracy of any conclusions and subsequent recommendations for both practice and research.

3.3.5.2 Funnel plots

To investigate the presence of publication bias, a funnel plot would be constructed including all studies selected for the review to visualise the distribution of studies from the line of no effect. This is a figure plotting any given trial's estimate of the intervention effect against a measure of the study's size or precision, such as the number of participants involved. The latter element is plotted on the vertical axis so that larger studies reside at the top of the graph. Because the precision of a study's estimate of the treatment effect increases as the size of the study increases, it is expected that smaller studies will be scattered towards the bottom of a funnel plot. Therefore, the figure should resemble a relatively symmetrical inverted funnel if there is a lack of bias present amongst studies.

An asymmetrical graph could be an indicator of publication bias, with the degree of asymmetry observed being related to the strength of the influence of bias. This is the case when smaller studies without statistically significant effects do not go to publication. It is important to note that some asymmetry could also be secondary to factors such as small sample sizes in trials or chance. Cochrane recommend that at least 10 trials should be included in a review for a funnel plot to discern meaningful results (103).

3.3.6 Measures of treatment effect

Dichotomous data, such as mortality rate for example, are analysed after first calculating effect sizes as odds ratios (OR) with 95% CIs. As it is common for study authors to use different measurement scales across different trials, standardised mean differences are calculated and presented with 95% CIs for continuous data (e.g. nutritional parameters). Time-to-event data are converted into hazard ratios (HR) with 95% CIs.

Where similar outcomes are reported within several included studies, these are collated into meta-analyses to distinguish an overall treatment effect, and forest plots drawn up to illustrate the strength of effect. These plots allow visual inspection for indicators of both publication bias, as mentioned, and to indicate the presence of heterogeneity of results.

3.3.7 Heterogeneity

It is important to assess included studies for both clinical heterogeneity and methodological heterogeneity. As previously mentioned, examining forest plots for any obvious lack of overlap of the CIs or estimated treatment effects between studies can indicate the presence of heterogeneity. A statistical test used in Cochrane reviews and commonly included in a forest plot is the chi² test which provides an indication of whether the differences between treatment effect estimates are down to more than random chance. When the chi² statistic is large relative to its degree of freedom, this evidences the presence of heterogeneity beyond random variation. Because the test can be of low power where a small number of studies are concerned, a statistically significant result can support the presence of heterogeneity, but an output that is not statistically significant cannot prove its absence (104).

The I² statistical test can be performed to further estimate the level of heterogeneity present using the following equation, where Q is the Chi² statistic and df is the degrees of freedom (105):

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

The following I² output ranges (105) could be used to approximate the level of heterogeneity across studies:

- 0-40%; may represent low-level heterogeneity
- 30-60%; may represent moderate heterogeneity
- 50-90% may represent substantial heterogeneity
- 75-100% considerable heterogeneity

The I² result should also be interpreted in the context of the magnitude and direction of the treatment effects as well as the p value used for the original chi² test (105).

We did not propose to undertake any subgroup analyses initially. For example, as CFRD is more common in adults, we did not automatically consider subgroup analysis by age as this

could have introduced bias, e.g. older people with CF might have different perceived benefits.

It was decided that, should it become apparent that there was substantial heterogeneity (identified through visual inspection of a funnel plot or through calculating I^2 values, denoted above) between studies, then we would consider removing relevant confounders for subgroup analyses such as sex or different models of CGM systems for example.

If at least ten studies were included for meta-analysis in the review, these would have been performed through use of the formal test for subgroup differences in the Review Manager 5 software (101).

3.3.8 Meta-analysis and sensitivity analysis

It was decided that a random-effects meta-analysis of studies deemed sufficiently similar for the results to be clinically important would be carried out. However, in the case of only one study being found to be eligible for inclusion in the review, it was agreed that it would be more appropriate to provide a narrative description of the single study's results.

Sensitivity analysis is an assessment of how various sources of uncertainty may have affected the overall certainty of any subsequent meta-analyses performed. If one or more studies which met the criteria for inclusion in the review were deemed to have a high risk of bias in one or more of the GRADE framework (GRADE) domains (106), the authors would then deem it necessary to perform a sensitivity analysis. This would involve excluding these studies and performing another meta-analysis with the new data set before comparing the meta-analyses for any impact these potential biases may have had on the results.

4. Results of the CFRD Cochrane systematic review

4.1 Context of the results

This work represents an original Cochrane systematic review in the process of being prepared for publication in collaboration with the Cochrane CFGD group. The basis of this study was guided by the “continuous glucose monitoring for monitoring cystic fibrosis related diabetes” topic on the group’s list of priority titles prior to authorising this review. An updated list of the group’s priority titles can be found on the Cochrane CFGD website (92).

4.2 Results of the selection process

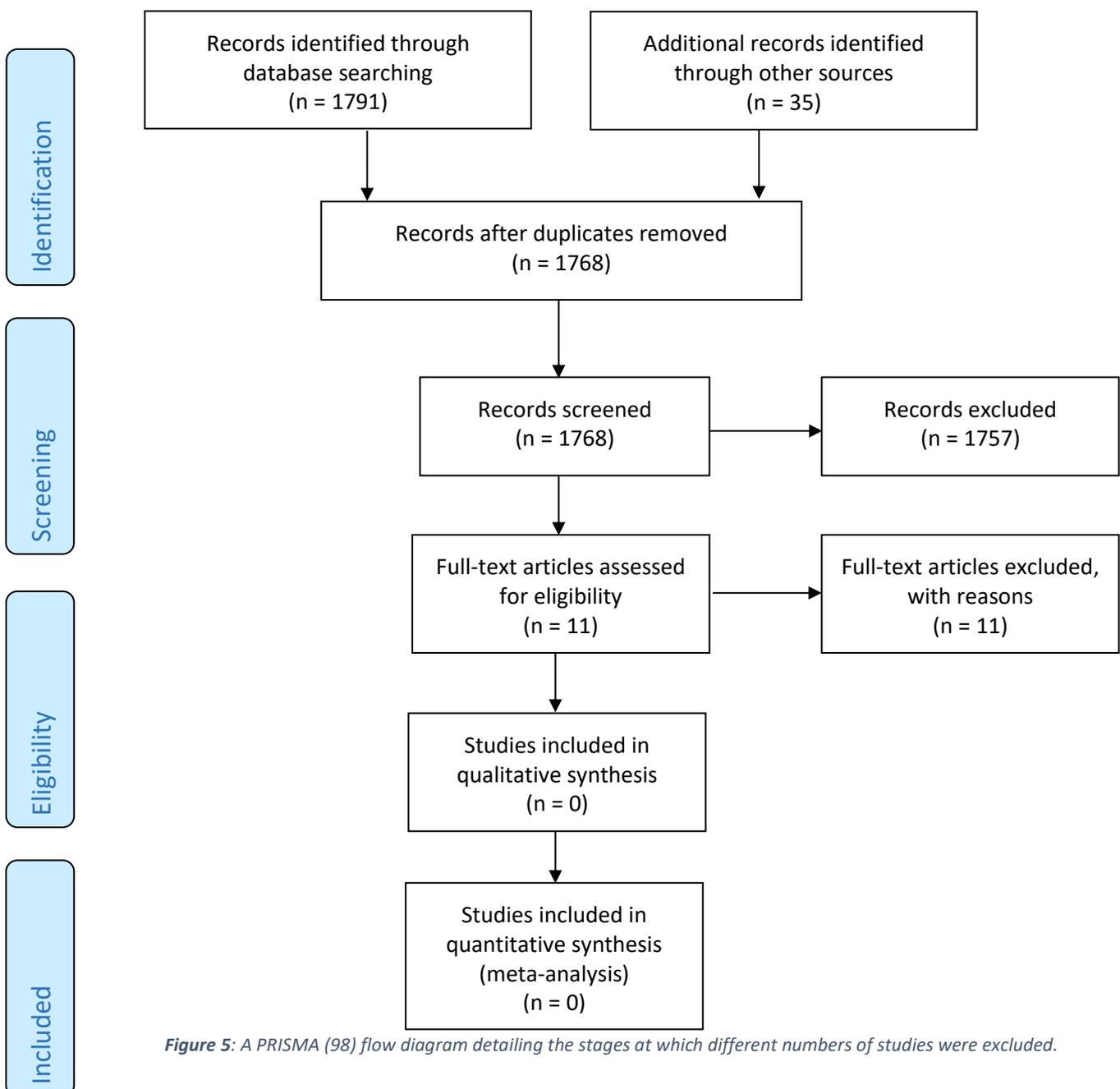


Figure 5: A PRISMA (98) flow diagram detailing the stages at which different numbers of studies were excluded.

4.2.1 Included studies

As illustrated above, out of a total of 1768 studies, once duplicates were eliminated, there were found to be no completed RCT studies that appropriately fit our protocol's criteria for inclusion in the review. The only study that did meet our criteria was a single RCT protocol (107) registered at *clinicaltrials.gov* (NCT03939065) that has not yet been undertaken, and thus, presented no data to be analysed for the review at this time.

4.2.2 Ongoing studies

From the data search process, we identified one RCT protocol, as mentioned above, registered at *clinicaltrials.gov* that could be eligible for inclusion in a future version of the Cochrane review (NCT03939065)(107). The RCT protocol, titled "*Sensor Augmented Pump (SAP) Therapy for Inpatient Management*", is sponsored by the University of Colorado in collaboration with the Cystic Fibrosis Foundation and has an approximate start date of June 2020 and estimated end date in February 2023 (NCT03939065). The pilot study plans to recruit 36 participants, between the ages of 8 and 25 years old, who are diagnosed with CFRD (based on ADA guidelines) and have been admitted for a pulmonary exacerbation.

The trial will investigate the effects of CGM combined with insulin pump therapy (otherwise known as sensor augmented pump (SAP) therapy) on inpatients with CFRD, with the aim of optimising glycaemic control (NCT03939065). Participants will be randomised and assigned to one of two parallel treatment arms through study completion, for up to three weeks. Those allocated to the experimental arm will have their glucose levels monitored by CGM and receive their insulin dosing via the pump (NCT03939065).

The control arm of the trial will consist of conventional diabetes management with multiple daily insulin injections (or an insulin pump where the patient was established on a pump in an outpatient setting) and CBG. Participants in the control arm will additionally wear a blinded CGM for outcome assessment. The outcomes they have stated they will report include differences in CGM percent time over 140 mg/dl, pulmonary function, circulatory inflammatory markers, weight, CBG level and beta-cell function (NCT03939065).

It is likely that a completed version of this trial will be included in a future update of this systematic review.

4.2.3 Excluded studies

From the original data search, 11 full text articles were excluded. Below, Table 1 outlines these studies and the reasons why they were removed from the study.

Study number and title	Study authors	Reason(s) for exclusion
1. "Cystic fibrosis-related diabetes in children--gaps in the evidence?" (108)	Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME.	1. Non-RCT (Review of literature) 2. CGM as a diagnostic tool
2. "Update on diagnosis and monitoring of cystic fibrosis-related diabetes mellitus (CFRD)." (109)	Noronha RMD, Calliari LEP, Damaceno N, Muramatu LH, Monte O.	1. Non-RCT (Review of literature) 2. CGM as a diagnostic tool
3. "A Practical Approach to Glucose Abnormalities in Cystic Fibrosis." (110)	Jones GC, Sainsbury CAR.	1. Non-RCT (Review of literature) 2. CGM as a diagnostic tool
4. "Screening for cystic fibrosis-related diabetes: a systematic review." (57)	Waugh N, Royle P, Craigie I, Ho V, Pandit L, Ewings P, et al.	1. Non-RCT (Systematic review) 2. CGM as a diagnostic tool
5. "Cystic fibrosis-related diabetes: optimizing care with a multidisciplinary approach." (111)	Frost F, Dyce P, Ochota A, Pandya S, Clarke T, Walshaw MJ, et al.	1. Non-RCT (Review of literature)
6. "Cystic Fibrosis-Related Diabetes." (37)	Kayani K, Raihan M, Hasan M.	1. Non-RCT (Review of literature)
7. "Automated glycemic control with the bionic pancreas in cystic fibrosis-related diabetes: A pilot study." (112)	Sherwood JS, Jafri RZ, Balliro CA, Russell SJ, Putman MS, Zheng H, et al.	1. Wrong study design (crossover trial)
8. "A service evaluation of the use of flash glucose monitoring in people with	Guilbert L, Arregui-Fresneda I, Daniels T, Holt RIG.	1. Non-RCT (retrospective case-notes review)

cystic fibrosis-related diabetes (CFRD).” (113)		
9. “294 Exploring the utility of continuous glucose monitoring (CGMS) for cystic fibrosis related diabetes (CFRD).” (95)	Jackson VM, Dyce P, Walshaw MJ.	1. Non-RCT (retrospective observational study)
10. “336 The impact of continuous glucose monitoring on HbA1c in patients with cystic fibrosis related diabetes.” (94)	Stackhouse CA, Floto R, Haworth CS, Shafi NT, Buczak V, Johnson CM, et al.	1. Non-RCT (single assignment study)
11. “Validation of continuous glucose monitoring in children and adolescents with cystic fibrosis: a prospective cohort study.” (65)	O’Riordan SM, Hindmarsh P, Hill NR, Matthews DR, George S, Greally P, et al.	1. Non-RCT (cohort study) 2. This study validated CGM for use in pwCFRD but made no link between the use of CGM and management of CFRD

Table 2: Table of articles excluded at the full text stage.

Four studies were excluded because they focussed on CGM as a method of diagnosing or screening for CFRD rather than monitoring the disease, three of which related to (non-systematic) reviews of established literature (108-110).

The first of which, published in 2010, lists CGM as one method of screening for and diagnosing CFRD, noting that hyperglycaemic peaks have been demonstrated via CGM in pwCF who have otherwise normal OGTTs and therefore CGM can detect hyperglycaemia earlier than OGTTs (108). In the same paper, Rana et al. describe a CGM readings of >7.8mmol/l for ≥4.5% of the time as being “associated with declining weight SD scores and lung function in the preceding year”(108). The authors go on to suggest that CGM could aid diagnosis of CFRD when used in conjunction with the OGTT and clinical judgement.

The second paper, by Noronha et al., made only one reference to the use of CGM which was in the context of diagnosing ‘indeterminate’ glycaemia which they described as “post-

prandial hyperglycaemia detected by continuous glucose monitoring (CGM), in the absence of symptoms suggestive of diabetes”(109).

In the third paper, Jones et al. also suggest the use of CGM as an adjunct to the OGTT to evaluate glucose at 1 hour post-glucose load as isolated hyperglycaemia at this point is known to affect lung function in CFRD (110).

The fourth study excluded, for investigating the diagnostic capabilities rather than the therapeutic monitoring usage of CGM, was an extensive systematic review of four major databases by Waugh et al (2012) which examined the methods of screening for CFRD and the effectiveness of available treatments (57). The authors suggested that because CGM is better at detecting hyperglycaemia, it may be the “best screening test” and become the gold standard for diagnosis in the future, with a caveat that further evidence on the topic is still required. The paper explains that trials investigating the effects of starting insulin at different stages of hyperglycaemia, beginning with post-prandial hyperglycaemia diagnosed through tests such as CGM. Waugh et al also wrote that further evidence on the “relative merits of the 1-hour GCT, CGMSs and serial profiles is required, with the aim being to detect any hyperglycaemia >8mmol/l” (57).

Another reference (111), written by Frost et al. (2019), was excluded as it consisted of a literature review rather than an RCT. The paper describes the integration of CGM data feedback with the efforts of the various CF MDT members, to devise an appropriate plan of care for pwCFRD. They hypothesise that, in the future, a CGM-informed tripartite approach to devising treatment plans by the advanced nurse practitioner, CF dietician and the pwCF themselves may become the ‘gold standard’ (111).

Reference number 6 in Table 1 (37) was also excluded due to being literature review. The 2018 paper by Kayani et al. comments on the 2016 paper by Bolinder et al. (114), which established the utility of CGM in the monitoring and management of T1DM, and extrapolated that CGM may therefore be a feasible alternative to CBG in CFRD. Said paper by Bolinder et al. presented no direct evidence to support this use of CGM in pwCFRD.

A pilot study (112), ruled out due to its crossover design and published this year by Sherwood et al, investigated the use of a ‘bihormonal bionic pancreas’, originally designed

for people with T1DM, in 3 pwCFRD. The device used CGMS guided monitoring of glucose levels to automate administration of insulin and glucagon accordingly. The second arm of the study involved an insulin-only setting of the same device, also linked to CGM data, whereas the third arm consisted of usual care. In people with T1DM, both interventions had previously been shown to reduce mean CGM glucose reading, with the bihormonal setting also reducing time spent in hypoglycaemic glucose ranges (112). Both configurations of the device lowered participants' mean glucose with minimal hypoglycaemia; the authors concluded that their results warranted further investigation of automated glucose regulation technology in pwCFRD (112).

Three studies (94, 95, 113) that focussed entirely, or in part, on the outcomes of using CGM guided treatment of CFRD were removed at the full-text stage due to having study designs that were incompatible with our criteria. This included a retrospective case-notes review, published in 2018 by Guilbert et al., of 145 pwCFRD, 16 of which had their treatment modified secondary to the CGM data and "led to clinical changes in a significant number of patients" (113).

The second of these three to be excluded, study 9 from Table 1 by Jackson et al., was a review of the reasons why 99 unrandomised instances of CGM in 85 people were carried out in a CFRD clinic, alongside patients' clinical outcomes 3-6 months after (95). Fifty-five patients received CGM for "ongoing management". The authors describe CGM as a useful educational tool to help pwCFRD and their carers to better understand their condition, as well as a "useful tool to aid the management of people with CF who already have [CFRD]" as the FEV₁ improved in 74% of those who had their treatment adjusted in response to CGM data, whereas 60% improved their weight in response (95).

The third article was about a single assignment study, by Stackhouse et al., of 11 pwCFRD who were failing to provide CBG data and was excluded since it did not follow an RCT design (94). Participants' insulin regimens were altered based on 3-day blinded CGM and followed up at 3, 6 and 12 months. This led to a "significant drop in HbA1c that was maintained for at least 12 months", leading the authors to conclude that CGM may be useful where collecting CBG data is difficult (94).

A final reference excluded at the full text stage referred to a cohort study aiming to validate the reliability, reproducibility and repeatability of CGM, in comparison to OGTT, to assess hyperglycaemia in 102 children and adolescents with CF (65). O’Riordan et al. concluded that CGM is a valid measure of glycaemia in children and adolescents with CF. Because this trial made no link between using collected CGM data and altering CFRD treatment, and because it was not an RCT study design, it was removed from the data collection process.

In summary, despite conducting an exhaustive literature review spanning five major databases, we have not identified any data from randomised controlled trials that have evaluated the impact of CGMS on the well-being of pwCF with CFRD.

4.3 Assessing risk of bias and the quality of evidence

Only one study was found to be potentially eligible for inclusion in this systematic review. However, as it relates to a protocol of a study yet to begin, the study was excluded at the screening stage and the data currently available is insufficient to accurately assess what the risk of bias would be.

If it had been the case that there had been studies included in the review, they would have been independently examined (by AT and AM) to determine the risk of bias present in each study as well as grade trials according to the GRADE criteria, which are outlined in the next section. Below is an example of how the results of the risk of bias assessments would be tabulated to allow a simple visual comparison of the relative strengths and weaknesses across studies; with green representing a low risk of bias, yellow signifying an unclear risk of bias, and red indicating a high risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Participant/ personnel blinding (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Study X	Green	Yellow	Green	Yellow	Green	Red	Green
Study Y	Yellow	Green	Green	Green	Green	Yellow	Green

Table 3: Example of a summary table of risk of bias outcomes following assessment of studies included in a hypothetical Cochrane review.

A figure such as Table 1 would also be associated with a further separate table for each included study. These additional tables would outline the specific reasons why a given study would be assessed as having a particular level of bias in each stated category, an example of which is demonstrated in Table 2 following on from fictional “Study X” in Table 1.

Domain of Bias	Authors’ Judgement	Reasoning
Random sequence generation (selection bias)	Low risk	E.g. An independent party generates a random sequence using a computer.
Allocation concealment (selection bias)	Unclear risk	E.g. Method of allocation concealment not stated.
Participant / personnel blinding (performance bias)	Low risk	E.g. Study personnel and participants were blinded to treatments Packaging and medications taken by participants were visually identical.
Blinding of outcome assessment (detection bias)	Unclear risk	E.g. Insufficient information supplied on the methods used to blind assessors and/or the effectiveness of this in practice.
Incomplete outcome data (attrition bias)	Low risk	E.g. All participants who were randomised were accounted for.
Selective reporting (reporting bias)	High risk	E.g. Multiple outcomes of interest stated in the protocol and recorded in the trial have not been reported in the final study publication.

Other bias	Low risk	E.g. The authors did not have any additional concerns
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Table 4: Example of a hypothetical risk of bias assessment explanation table for "Study X".

4.3.1 The GRADE framework

The GRADE framework was developed by the GRADE Working Group which is made up of a variety of health care personnel including clinicians, researchers, guideline developers and public health officers (106). The framework aims to provide a consistent, transparent criteria to assess the quality of evidence and the strength of guidelines by which healthcare decisions are made (106), and is endorsed by over 100 organisations globally (115). The meanings of the four levels of evidence scoring are demonstrated below.

GRADE score	Meaning of the score
High certainty	One can be very confident that the true effect lies close to the estimate of the effect.
Moderate certainty	The true effect and the estimate are likely to be close, but there is a possibility that they are substantially different.
Low certainty	Confidence in the effect estimate is limited, the true effect and the estimate may be substantially different.
Very low certainty	There is very little confidence in the findings: the true effect is likely to be substantially different from the estimate.

Table 5: The four levels of evidence in the GRADE framework

RCTs, as discussed, are often held as the gold standard for producing low-bias evidence (74) and as such, the GRADE framework starts with RCTs graded at 'high certainty' and non-randomised studies at 'low certainty' (106).

In the case of meta-analysis or narrative synthesis, reviewing certain elements of studies can raise or lower the certainty of the conclusions drawn by that study. Factors that may lower the GRADE score of a study include (115):

- Overall risk of bias across studies that contribute data for an outcome.
- Inconsistency: where there are widely differing estimates of effect, for example, owing to heterogeneity.
- Indirectness: where studies do not directly answer or apply to the review question
- Imprecision: Where there are few participants or events across studies, or particularly wide confidence intervals. As a rule of thumb, having less than 400 people or events across studies warrants consideration of a GRADE level being dropped (106).
- Publication bias: to consider dropping a GRADE level due to publication bias, there must be strong suspicion of selective publication of studies or outcomes, and this can only result in a maximum drop of one certainty level.

Where there are no concerns about the above aspects, the GRADE level should not be rated down, though serious concerns about any domain listed can cause a rating to drop one level, or two levels where there are very serious concerns about these elements (115).

On the other hand, in rare circumstances, the level of GRADE certainty can be raised, including in the case of a dose-response gradient or where a large relative effect is demonstrated (rated up by two levels where this is ≥ 5 , or by one where it is < 5 but > 2)(106).

4.4 Effects of interventions

Only one paper was identified as having potential for inclusion in this review. As it is an ongoing trial with no current results, it was excluded and therefore no studies with outcome data have been included for review. This means that the effect of using CGMS to guide insulin therapy modification in the context of CFRD currently remains undetermined.

4.5 Summary of results

This Cochrane review identified no current RCT data, evaluating the utility of CGMS in the context of CFRD, out of 1768 initial results. One registered protocol for an RCT was identified

as meeting the criteria for inclusion, however, they have not yet collected any data. Once available, this study will be fully assessed for quality and data included if appropriate.

4.6 Overall completeness and applicability of evidence

We identified an absolute lack of relevant evidence to answer the review question, regarding the effect of using CGM to titrate insulin regimes in pwCFRD. Most studies examining the use of this intervention are in people with T1DM (87), including a Cochrane review (79, 85, 87), but there remains no evidence about its applicability for pwCFRD in this context.

4.7 Potential biases in the review process

Cochrane methodology was adhered to minimise the risk of bias throughout each step of the review. This included producing a protocol to be published after peer review and performing a comprehensive search of the Cochrane CFGD Group's register of CF related trials, both complete and ongoing.

The total resulting studies of the literature searches were independently assessed by authors AT and AM using the predetermined inclusion criteria outlined in the protocol, before extracting data and grading the risk of bias in included studies would be done. These steps were all undertaken in a parallel fashion by AT and AM, with any discrepancies then being resolved through joint discussion, or mediation by a third author where necessary. Analysis of the data would then have been performed using Review Manager software (101).

The authors are aware of the possibility that our search may have retrieved fewer records than we intended due to the inaccessibility of the WHO ICTRP. However, this database is regularly searched for RCTs which are then added to the Cochrane CENTRAL trials register(116) which was included as part of our search strategy, making it less likely that relevant trials have been missed.

This situation will continue to be monitored and, if the circumstances change, the database will be searched for any relevant trials before publication of the full review if possible.

4.8 Agreements and disagreements with other studies or reviews

There is a published protocol for a 'diagnostic-test accuracy' style Cochrane review examining continuous glucose monitoring systems for the diagnosis of cystic fibrosis-related diabetes (91). We are not aware of any published systematic reviews of RCTs evaluating the impact of CGM on the management of, and subsequent outcomes observed in people with CFRD.

4.9 Creating a framework for future studies

Having demonstrated the lack of research currently available to determine the impact of CGM on the management of pwCFRD, a collaborative discussion was held to determine how future studies could best go about producing a robust evidence base on this topic. This included both an independent chair and the author group for this review which consists of; a CFRD specialist Advanced Nurse Practitioner, a respiratory consultant, a respiratory medicine trainee doctor, and a medical student/postgraduate researcher. The final member of the team, another medical student, was unavailable for the initial meeting.

Our aim was to determine a framework for research on this topic to expand the current knowledge base. Details of the resulting recommended study characteristics are included in the discussion chapter of this thesis.

5. Discussion

The main body of this work centres around an original Cochrane systematic review designed to investigate the impact of continuous glucose monitoring systems on the lives of pwCFRD. They were specifically investigated with reference to how data collected through CGMS leading to alterations to a person's insulin regime, e.g. dosage, type of insulin, number of doses; may affect their outcomes, both clinical and non-clinical. This was compared to outcomes observed following insulin titration secondary to traditional therapy i.e. guided by CBG or HbA1C.

As CFRD is becoming more prevalent due to factors such as the improving life expectancy of pwCF; the impact of CFRD on peoples' lives is of increasing importance, as is research into ways to help alleviate treatment and disease burden for individuals. As part of this, it is imperative to ensure that these new technologies are properly evaluated and information about their effectiveness is kept up to date. Creating and maintaining a sturdy body of evidence supports the decision-making of policy makers, clinicians, and patients alike.

CGMS is an expensive resource, particularly in comparison to the use of the CBG method (117) and cost-effectiveness is an important consideration for policy makers. More research is needed to determine a clear evidence base upon which to support widespread implementation of CGMS for the management of CFRD if it is shown to be appropriate and economically feasible to do so.

This could be especially pertinent for pwCFRD in countries such as the USA where personal medical costs and insurance coverage may present further barriers to the availability and uptake of new interventions, even when they are shown to be beneficial (87). This issue is relevant globally; a robust evidence base encourages funding and allows clinicians to get access to these treatments for their patients.

5.1 Summary of findings

The results of this study indicate that the evidence currently available is insufficient to determine the impact of continuous glucose monitoring on the management of people with cystic fibrosis-related diabetes.

Throughout the data collection and literature review performed for our Cochrane review, there was found to be a growing number of studies aiming to evaluate the utility of CGM as a diagnostic test for CFRD and/or deciding when to first initiate insulin therapy (56, 64, 65, 91), yet recommendations across guidelines have remained relatively nonspecific (14). There was limited literature relevant to the use of CGM as an aid to managing the treatment regimens of pwCFRD who already take insulin as demonstrated by the results of our Cochrane review.

One reason for this is the lack of clinical trial data on the best approach for treatment of CFRD with no clear consensus on which type, frequency or mode of delivery of insulin is best for pwCFRD (28, 59). A 2016 Cochrane review, comparing different types of long or short acting insulin as well as oral hypoglycaemic agents for the treatment of CFRD, acknowledged that insulin therapy is the most widely used therapy for CFRD, as endorsed by the Cystic Fibrosis Foundation (118, 119). The same review found no significant conclusive evidence that any one of these treatments conveyed more benefit to pwCFRD than another in terms of stabilising hyperglycaemia and improving outcomes (118).

This uncertainty is echoed within the ADA clinical care guidelines for CFRD where they endorse the use of clinical judgement to discern the best regimen for individual patients, and acknowledge the lack of evidence surrounding comparative superiority of specific insulin regimens in CFRD (28). There is a lack of consistency in how clinicians diagnose CFRD, when insulin treatment should be initiated, and what regimen is best to treat pwCFRD. These factors likely contribute to issues for researchers designing studies to evaluate the effectiveness of types of glycaemic data collection, such as CGM, upon which these many decisions are usually based.

In the context of this Cochrane review, CGM was not being evaluated as a stand-alone test, but rather as an adjunct to treatment. To some degree, CGM can only impact clinical outcomes when linked to a defined and proven treatment protocol stipulating how the patient should be treated for any given excursion in blood glucose. Additionally, real-time CGM has potential to act as an intervention to help educate pwCFRD on how their treatment affects their glucose levels. There is potential for this intervention to empower pwCFRD to understand their condition better and take more control over how to respond to trends in

glucose rather than just individual CBG glucose readings, as has been demonstrated in other diabetic populations (120).

Conversely, there is concern that this aspect of real-time CGM could negatively impact pwCFRD, as having nearly 24-hour information on their glucose levels could present a burden. Through stakeholder engagement it was made clear that there were concerns that the almost constant knowledge of the direction of glucose trends could trigger some pwCFRD to try to 'chase' the numbers, when permanently maintaining normal glucose levels is unrealistic and associated with a risk of hypoglycaemia (121). It is important that the potential distress of this continuous stream of data is considered and evaluated; particularly for pwCFRD, who already face a significant burden of treatment and reduced quality of life compared to their non-diabetic counterparts. As such, it is important that further research examines the complex psychological implications of CGM use to ensure that it is implemented in a way that is most beneficial to pwCF.

5.1.1 Available evidence

Though it was unfortunate that our protocol's rigidity meant our searches did not find any studies eligible for inclusion in the review, some of the non-RCT studies that were excluded at the 'full text' stage, outlined in chapter 4.2.3, did add important knowledge pertaining to CFRD.

Waugh et al.

Although it focussed on the diagnostic capabilities rather than the therapeutic monitoring usage of CGM, the extensive systematic review by Waugh et al also reviewed the effectiveness of available treatments for CFRD (57). While including a caveat that further evidence on the topic is still required, there was a suggestion that CGM is better at detecting hyperglycaemia in a diagnostic context than other forms of glucose monitoring, i.e. CBG and OGTT (which is assessed via CBG). This reflects that CGM could be more capable of identifying abnormal peaks than CBG in the context of monitoring in pwCF who already have a CFRD diagnosis on an ongoing basis, but further research would be necessary to confirm this.

Sherwood et al.

Ruled out due to its crossover design, Sherwood's paper investigating the use of CGM-driven automated glucose regulating technology in 3 pwCFRD. While this was a small pilot study, the results were exciting given that the device lowered participants' mean glucose without triggering any major hypoglycaemia and was a treatment that participants found acceptable (112). Despite this, the study needs to be interpreted with caution given the small sample size and crossover nature of the trial and thus the potential for the effects of one intervention having interfered with the results of the next intervention. Another concern is that while the authors were examining a version of CGM-led insulin therapy, their focus was directed at the use of sensor augmented pump therapy rather than the benefit of CGM specifically. Still, further studies in this area, such as trial denoted by the protocol described in section 4.2.2 (107), have the potential to expand our current knowledge base on CGM directed management of CFRD.

Guilbert et al.

This study focussed on the clinical utility of 'flash' CGM, with 145 pwCFRD involved. Sixteen people had CGM to change/affirm treatment and six people had CGM to support engagement with treatment. The paper claims that changes made secondary to CGM "led to clinical changes in a significant number of patients", however the only format available for this retrospective case-notes review was a journal abstract, limiting the utility of its data (113).

Jackson et al.

This conference abstract reviewed the reasons why 99 unrandomised instances of CGM in 85 people were carried out in a CFRD clinic (95). The authors describe CGM as a useful educational tool to help pwCFRD and their carers to better understand their condition, as well as a "useful tool to aid the management of people with CF who already have [CFRD]" (95). Despite this, Jackson et al. do not provide the criteria by which they determined this, nor statistical data to back up the otherwise anecdotal evidence. Upon contacting the authors for further information, a poster version of the data was received with no further information available, again limiting the utility of the data of the work.

Stackhouse et al.

Another article available only as an abstract, this work described how 11 pwCFRD who were failing to provide CBG data had their insulin regimens altered based on an isolated 3-day blinded CGM (94). The significant drop in HbA1c that was maintained for at least 12 months in these patients is a positive finding that could indicate the utility of CGM-led insulin therapy in pwCFRD who are needle phobic or may struggle to take CBG readings as often as recommended or at all (94). The concept that one 3 day period of CGM could make such a substantial and sustained difference to measures of hyperglycaemia raises the question of how daily, or almost daily, CGM use could impact the management of pwCFRD. It is recognised that this study also had quite a small sample size and that, again, further evidence is required on the topic.

O’Riordan et al.

Although this cohort study by O’Riordan made no link between using collected CGM data and altering CFRD treatment, the validation of the reliability, reproducibility and repeatability of CGM in assessing hyperglycaemia pwCF (65) is incredibly important for the development of further research on this topic. Proving that CGM can be used to accurately reflect blood glucose is a key element in being able to perform trials on CGM data-led management alterations.

5.2 Development of outcome measures for this review

The James Lind Alliance (JLA) engages with groups of stakeholders to explore and prioritise the uncertainties and unanswered questions that surround a specific area of health, such as CF. These groups are called priority setting partnerships (PSPs) and include patients, carers and health and social care professionals whose perspectives are consulted to compile the top 10 priorities list (the full list of which can be found in the appendix)(90). The goal of this process is to steer researchers and allocation of funding in the direction of addressing the issues which are directly relevant and likely to be of the most benefit to both people living with an illness and those involved with caring for someone who does. The PSP for pwCF established that the number one priority is determining effective ways of simplifying their large treatment burden (89, 90).

These priority areas were considered during the outcome development process for this review, in particular; investigating ways of simplifying the treatment burden and helping to

delay or prevent the progression of lung disease in early life in people with CF (90). Consequently, this resulted in the inclusion of both percentage change in FEV1 (as a marker of lung disease) and the burden of treatment experienced by pwCFRD as outcomes of interest to help address these issues.

To further ascertain what our main outcomes of interest would be for this review; research was also conducted into the outcomes deemed most important by pwCFRD and their families as well as the clinicians involved in their care. Initially, clinicians from the CF team in Alder Hey Children's Hospital were consulted regarding what parameters they felt to be most pertinent to the ongoing assessment of CFRD. These were largely clinically measured outcomes such as lung function and CFRD (or CFRD treatment) related adverse effects.

As part of the stakeholder engagement process, author AT conducted semi-structured interviews with pwCFRD and their families/carers; exploring what aspects of their treatment mattered the most to them. Interestingly, this highlighted the impact of more personal factors on pwCFRD, especially the burden of treatment and quality of life they experience. Those consulted also emphasised nutritional parameters, especially weight, as a key element of their own monitoring of their conditions, both CF and CFRD. They often linked maintenance of body mass with better lung function, a lower rate of respiratory infections and being an indicator that their diabetes was under control, as backed up by the research data detailed in the first chapter of this thesis (7, 11, 14, 15, 19-22, 43). This helped shift our focus to outcomes that are not strictly clinically imperative, but that have significant impact on the lives and wellbeing of pwCFRD.

5.3 Limitations

This work represents an extensive literature review. However, as touched upon in the methodology chapter, the advent of the COVID-19 pandemic impacted elements of this work.

Firstly, the publication of the protocol was delayed due to the nationwide disruption caused by lockdown and the associated reduction in staffing and an increase in workload across most organisations.

We were also unable to access the WHO ICTRP due to COVID-19; however, the Cochrane CENTRAL clinical trials registry, which is regularly updated with relevant records for RCTs or quasi-RCTs listed in the ICTRP, was searched for the purposes of this systematic review.

These issues first occurred during the initial data collection phase of the Cochrane review, mandating that this database was omitted for the purposes of this thesis due to time constraints. Despite this, we will still endeavour to incorporate search results from the original ICTRP into the final systematic review before submission for publication.

5.4 Implications for clinical practice

No randomised controlled trials were identified to evaluate the impact of continuous glucose monitoring systems on the management of people diagnosed with cystic fibrosis related diabetes. As a result, it is not currently possible to draw reliable conclusions on the potential benefits or harms of CGMS-guided insulin regimes in pwCFRD.

In people with T1DM, Bolinder et al. have shown that CGM reduced hypoglycaemia and the number of CBGs required per day, making it a plausible and highly acceptable alternative to CBGs in this population (114). CFRD has a distinct pathophysiology to T1DM, thus caution should be taken in extrapolating the observed effects of CGM on the management of people with T1DM to the presumed impact the technology will have on management of pwCFRD.

While the lack of research surrounding the impact of CGM in pwCFRD means that there is no evidence of potential benefits of the intervention, it equally has not explored any possible associated adverse effects. This means that any current use of CGM in the context of CFRD is likely based on evidence that is anecdotal (111) or extrapolated from research pertaining to its use in other forms of diabetes.

There is a need to accurately and transparently evaluate any adverse effects of using CGM both in general and in pwCFRD (122). For example, if the CGMS malfunctions or the algorithms incorrectly process the data, inappropriate modifications to insulin dosages could be made resulting in clinically significant adverse events (62). Individuals using closed loop SAP therapy are particularly at risk of this (62, 122). Use of CGMS is known to be associated with skin-related issues, usually localised to the sensor insertion site, such as contact dermatitis (62). Other issues reported include bleeding, pain, and allergic reactions (62, 123).

As discussed, there is currently no evidence to support the costly implementation of CGM to manage CFRD, although there are indications that CGMS are already being used in this context in some countries, such as the United Kingdom (111).

5.5 Implications for research

As discussed, there are currently no data available on the impact of CGM on the management of pwCFRD. Absence of evidence is not necessarily evidence of absence of effect, and therefore it is hoped that publication of this review will raise the profile of the question at hand and generate sufficient research to provide improve the evidence base.

In addition to assessing the technological advancement of glucose regulating therapies, in building upon the stakeholder engagement that was undertaken for this review, it is apparent that there is a need for further qualitative research to be performed to examine the qualitative aspects of the experience of pwCFRD and to further ascertain what outcomes truly make the most difference to their lives. Large scale qualitative studies carried out in a similar fashion to the JLA's PSPs (90) where as many stakeholders as possible are consulted until no new themes appear, can help ensure that no key concerns are overlooked. This kind of study could be greatly beneficial in guiding future trials in the direction of assessing appropriate outcomes to help elicit which therapies maximise benefit and minimise harm to pwCFRD.

As technology changes and is updated rapidly, there is a need for research to stay abreast of these developments, to ensure that the available evidence stays relevant and robust. The Cochrane Collaboration policy is that reviews should be updated every two years or less, or a commentary explaining why this has not been the case should be included (59). Once the aforementioned included RCT protocol (107) is completed, it may be appropriate to conduct an update of this review. Future versions of this review could also explore a cost-benefit analysis of CGM versus traditional methods of CFRD monitoring such as CBGs.

CFRD is a complex condition that mandates the addition of treatments such as insulin schedules on top of all of the therapies already involved in managing CF on a daily basis. Research to explore ways to reduce the burden of treatment experienced by pwCF and pwCFRD is imperative (90). Investigation into CGM in this context should be a priority as it

potentially may offer an alternative to the burden of multiple daily uncomfortable CBGs, or help prevent increasing burden of treatment and burden of disease secondary to CFRD specific complications through its theoretical potential to improve long term glycaemic control (79). For these reasons, further research in this area could also help address the JLA's sixth research priority in evaluating CGM as a technology with the potential to help motivate and support pwCFRD to improve and sustain adherence to their treatments (90).

In some cases, CGM is already in use within clinical practice settings (37), it has been implemented by some specialist advanced nurse practitioners in the context of CFRD for ongoing monitoring as well as instigation and titration of insulin therapy (37, 111). This further highlights the need for comprehensive investigation into the benefits and harms this may confer to pwCFRD in order to adequately support an evidence-based medical approach and help patients, clinicians and other stakeholders make informed decisions regarding the use of CGM for CFRD. With this in mind, the authors conducting this review propose a potential trial design below to address the review question.

5.5.1 Discussion of future trial formats

The recommended design would consist of a randomised controlled trial including people with a formal diagnosis of CFRD, of at least 6 to 8 years of age. This approximate age was suggested due to the cooperation required from patients in the measurement of outcomes such as FEV₁ (124), as the validity of the outcomes is paramount whilst still tracking from a relatively early stage of the condition (2). We would hope this lower age limit would help prevent unnecessary exclusion of children who have been appropriately diagnosed before the age of ten; the recommended age for annual screening (125). It was thought that a registry-based study with a specific strategy of monitoring and associated management would be necessary to yield more accurate results in terms of the effect that CGM has on the management itself. It would also be ideal for a trial to have a lengthy follow-up period for the assessment of long-term outcomes such as lung function and microvascular disease as these changes can happen slowly over time (31), though it is recognised that the practicality of monitoring participants for up to 10-15 years in order to assess such outcomes may be limited. For this reason, if it were to be shown that CGMS could significantly reduce hyperglycaemia, it may be feasible to consider this as a surrogate outcome for some longer-term outcomes. If hyperglycaemia can be consistently controlled, it is likely that the

incidence of CFRD complications, such as microvascular disease, will also be reduced. The other outcomes of interest would consist primarily of those listed in this review.

Such a study would focus on the impact of using CGMS-collected data to make adjustments to an individual's CFRD treatment, such as insulin dosage or frequency as discussed in this work. Alternatively, a future study could seek to find whether manipulating the diet of pwCFRD can prevent the significant peaks and troughs often picked up via CGMS data collection. If this could be shown to help stabilise control of blood sugars or even reduce the need for insulin, this could potentially have a significant positive impact on the treatment burden of pwCFRD as well as improving long term outcomes by reducing both hypo- and hyperglycaemia.

Previous studies of CGM technology have demonstrated the potential for variability in effect across different diabetic populations (79), highlighting the need for future research to encompass investigating the impact of CGM on different demographics within the population of pwCFRD i.e. across different age groups and during pregnancy.

In terms of prospective study designs, it was considered that participants could be randomised to a two or three-armed approach. The various possible combinations in each case are detailed below in Tables 4 and 5.

Intervention Arm	Control Arm
Real time CGM (i.e. FreeStyle Libre)	CBG
Blinded CGM	CBG
Real time CGM	Blinded CGM

Table 6: Possible interventions arms for a two-armed RCT investigating the use of CGM for CFRD.

Initially, it could be preferable to investigate either real-time or retrospective CGM compared to a control group, using CBG. This could help to first establish the impact of these devices under the umbrella of CGMSs as an intervention for CFRD compared to current standard treatment (28), before conducting research into any merits and/or issues the two sub-types may present when compared against one another.

Arm 1	Arm 2	Arm 3
CBG	Real-time CGM	Blinded CGM (with CBG QDS)

Table 7: Possible interventions arms for a three-armed RCT investigating the use of CGM for CFRD.

CGMSs can also be used ‘continuously’, i.e. daily or almost daily, versus ‘intermittently’, for example in the case of pwCFRD who normally use the CBG method to monitor their glucose levels but undergo a period of CGM to support changes to their diabetes treatment. These constitute two related but separate implementations of CGMS, and research into the impact of both applications on the monitoring and management of pwCFRD is warranted. Still, it is perhaps worth noting that in non-CF diabetic patients, to get the most benefit from CGM, the ADA recommends that the technology is used “as close to daily as possible”, with CGMSs being scanned at least every 8 hours (62). In addition to this, a Cochrane review on CGM in people with T1DM described indications that higher compliance with wearing CGMSs improves markers of hyperglycaemia to a greater extent (79).

Taking these findings into account, it could be reasonable to prioritise the ‘continuous’ application of CGM when devising future studies. For example, in a population of pwCFRD, ‘continuous’ CGMS could be compared with another form of CGM or another method of blood sugar monitoring such as CBG. In pursuit of identifying the impact of CGMS on pwCFRD, the resulting short and long term outcomes associated with this could then be examined, including quality of life, lung function and adverse effects as previously described in this work.

5.5.2 Limitations when devising studies

A confounding issue noted surrounding the suggested study designs is that where participants might be randomised to a blinded CGM arm, CBG could be required up to QDS for calibration of the device (126). This is a complex limitation as even if this calibration was not necessary, the use of a blinded CGM with no real-time data (from CGM or CBG) would still present an ethical issue of leaving a patient who is taking insulin without means of checking their glucose levels, and inappropriately leaving them vulnerable to hypoglycaemic episodes.

The inability to completely mask participants and study personnel from the allocated intervention, for example due to the nature of CGM sensors needing to be inserted into the skin, is a recognised issue across glucose technology studies to which there is no practical resolution (114, 127). The potentially increased risk of bias associated with this problem should be kept in mind and care must be taken when interpreting the findings of such studies, with both the strength and validity of the outcomes as well as the duration of such a trial taken into account.

6. Conclusion

This is the first systematic review to examine the impact of continuous glucose monitoring on the management of people with cystic fibrosis-related diabetes. The outcomes selected for the review were determined following stakeholder engagement with a variety of clinicians and health care professionals, as well as pwCFRD and their families. The selected outcomes focused on identifying meaningful differences to the lives and wellbeing of pwCFRD, not just surrogate clinical parameters.

Despite a comprehensive literature search of five major databases, no trials were identified to evaluate the effect of using CGM to monitor and manage CFRD. This search identified one protocol for an RCT, scheduled to begin recruiting participants later this year, as being potentially eligible for inclusion in a future update of this review (107).

This review highlights the need for a significant amount of research in this area to address the current gap in knowledge. As a result, a proposed future framework for clinical trials has been produced; investigative studies on this topic would ideally follow an RCT design and engage in long-term assessment of the outcomes that are relevant to pwCF.

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Appendices

[Blank summary of findings table for studies included in the Cochrane systematic review](#)

Intervention A compared with placebo/intervention B for condition						
Patient or population: Patients with Cystic Fibrosis Related Diabetes						
Settings:						
Intervention: CGMS-directed insulin therapy						
Comparison: standard insulin therapy (e.g. CBG-led)						
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard Therapy	CGMS-directed therapy				
Quality of Life Scale: units Follow up: up to x months or years, etc.						
Treatment-related adverse outcomes (e.g. hypoglycaemia (defined as ≤ 3.8 mmol/L), contact dermatitis etc) Scale: complete units to be used						

<p>Follow up: up to x months or years, etc.</p>					
<p>CFRD-related adverse outcomes</p> <p>Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Nutritional parameters</p> <ul style="list-style-type: none"> • Weight (kg or percentile) • BMI percentile <p>Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Self-efficacy</p> <p>Scale: complete units to be used</p>					

<p>Follow up: up to x months or years, etc.</p>					
<p>Burden of treatment Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Time off school or work (self-reported or otherwise documented) Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Change in Percentage Forced Expiratory Volume in one second (FEV₁) and/or absolute values in L</p>					

<p>Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Time in range (proportion of time within a normal blood sugar profile)</p> <p>Scale: complete units to be used</p> <p>Follow up: up to x months or years, etc.</p>					
<p>Abbreviations: CGMS (continuous glucose monitoring systems), CFRD (cystic fibrosis related diabetes)</p>					
<p>GRADE Working Group grades of evidence</p> <p>High certainty: One can be very confident that the true effect lies close to the estimate of the effect.</p> <p>Moderate certainty: The true effect and the estimate are likely to be close, but there is a possibility that they are substantially different.</p> <p>Low certainty: Confidence in the effect estimate is limited, the true effect and the estimate may be substantially different.</p> <p>Very low certainty: There is very little confidence in the findings: the true effect is likely to be substantially different from the estimate.</p>					

Full search strategy

Database/ Resource	Strategy
Embase Healthcare Databases Advanced Search (HDAS)	<p>#1 (cystic fibrosis).ti,ab,if,sh</p> <p>#2 (mucoviscidos*).ti,ab,if,sh</p> <p>#3 cystic* ADJ10 (fibro*).ti,ab,if,sh</p> <p>#4 fibrocyst* ADJ10 (pancrea).ti,ab,if,sh</p> <p>#5 "CYSTIC FIBROSIS"/</p> <p>#6 (1 OR 2 OR 3 OR 4 OR 5)</p> <p>#7 diabetes OR glucose OR insulin OR sugar OR (CFRD).ti,ab,if,sh</p> <p>#8 exp "DIABETES MELLITUS"/</p> <p>#9 (7 OR 8)</p> <p>#10 (6 AND 9)</p> <p>#11 (guide OR guided OR test* OR monitor OR monitoring OR manage OR management OR led OR CGMS).ti,ab,if</p> <p>#12 (10 AND 11)</p> <p>#13 "RANDOMIZED CONTROLLED TRIAL"/</p> <p>#14"CONTROLLED CLINICAL TRIAL"/</p> <p>#15 (random*).ti,ab</p> <p>#16 RANDOMIZATION/</p> <p>#17 "INTERMETHOD COMPARISON"/</p> <p>#18 (placebo).ti,ab</p> <p>#19 compare OR compared OR (comparison).ti</p> <p>#20 (evaluated OR evaluate OR evaluating OR assessed OR assess) AND (compare OR compared OR comparing OR comparison).ab</p> <p>#21 open ADJ (label).ti,ab</p> <p>#22 (double OR single OR doubly OR singly) ADJ (blind OR blinded OR blindly).ti,ab</p> <p>#23 "DOUBLE BLIND PROCEDURE"/</p> <p>#24 (parallel group*1).ti,ab</p> <p>#25 crossover OR (cross over).ti,ab</p>

	<p>#26 (assign* OR match OR matched OR allocation) ADJ5 (alternate OR group*1 OR intervention*1 OR patient*1 OR subject*1 OR participant*1).ti,ab</p> <p>#27 assigned OR (allocated).ti,ab</p> <p>#28 controlled ADJ7 (study OR design OR trial).ti,ab</p> <p>#29 volunteer OR (volunteers).ti,ab</p> <p>#30 "HUMAN EXPERIMENT"/</p> <p>#31 (trial).ti</p> <p>#32 (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)</p> <p>#33 ((random* ADJ sampl*) ADJ7 ("cross section*" OR questionnaire*1 OR survey* OR database*1).ti,ab) NOT ("COMPARATIVE STUDY"/ OR "CONTROLLED STUDY"/ OR (randomi?ed controlled).ti,ab OR (randomly assigned).ti,ab)</p> <p>#34 "CROSS-SECTIONAL STUDY"/ NOT ("RANDOMIZED CONTROLLED TRIAL"/ OR "CONTROLLED CLINICAL STUDY"/ OR "CONTROLLED STUDY"/ OR (randomi?ed controlled).ti,ab OR (control group*1).ti,ab)</p> <p>#35 ((case ADJ control*) AND random*) NOT (randomi?ed controlled).ti,ab</p> <p>#36 Systematic review NOT (trial OR study).ti</p> <p>#37 nonrandom* NOT (random*).ti,ab</p> <p>#38 ("Random field*").ti,ab</p> <p>#39 random cluster ADJ3 (sampl*).ti,ab</p> <p>#40 ((review).ab AND (review).pt) NOT (trial).ti</p> <p>#41 ("we searched").ab AND ((review).ti OR (review).pt)</p>
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	<p>#42 ("update review").ab</p> <p>#43 databases ADJ4 (searched).ab</p> <p>#44 (rat OR rats OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset*1).ti AND "ANIMAL EXPERIMENT"/</p> <p>#45 "ANIMAL EXPERIMENT"/ NOT ("HUMAN EXPERIMENT"/ OR "HUMAN"/)</p> <p>#46 (33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45)</p> <p>#47 32 NOT 46</p> <p>#48 (12 AND 47)</p>
<p>Web of Science Core Collection (Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC)</p>	<p>[Advanced Search]</p> <p>#1 TS=(cystic fibrosis)</p> <p>#2 TS=(mucoviscidos*)</p> <p>#3 TS=(cystic* NEAR/10 fibro*)</p> <p>#4 TS=(fibrocyst* NEAR/10 pancrea*)</p> <p>#5 #4 OR #3 OR #2 OR #1</p> <p>#6 TS=(diabetes OR glucose OR insulin OR sugar OR CFRD OR CRD**)</p> <p>#7 #6 AND #5</p> <p>#8 TS=(guide OR guided OR test* OR monitor* OR manage OR management OR led OR CGMS OR CGM)</p> <p>#9 #8 AND #7</p> <p>#10 TS=(trial* OR stud* OR control* OR random* OR cross* OR factorial* OR blind* OR mask* OR dummy OR assign* OR doubl* OR singl* OR tripl* OR trebl* OR placebo OR allocat* OR volunteer* OR group* OR compar*</p>

	OR match*) #11 #10 AND #9
Clinicaltrials.gov	[Advanced Search] CONDITION/ DISEASE: Cystic Fibrosis Diabetes OR cfrd OTHER TERMS: guide OR guided OR test OR testing OR monitor* OR manage OR management OR CGMS OR led OR adjust OR adjusted OR modify OR modified STUDY TYPE: Interventional Studies
Australian New Zealand Clinical Trials Registry (ANZCTR)	[Advanced Search Form] REGISTRY: ANZCTR HEALTH CONDITION(S) OR PROBLEM(S) STUDIED: diabetes CONDITION CATEGORY: Human Genetics and Inherited Disorders CONDITION CODE: cystic fibrosis
WHO ICTRP	[Advanced Search Form] TITLE: diabetes OR CFRD OR CFD and CONDITION: cystic fibrosis RECRUITMENT STATUS: All

The James Lind Alliance's cystic fibrosis PSP's top 10 research priorities (2017)

1. Finding effective ways of simplifying the treatment burden experienced by pwCF.
2. Relieving gastro-intestinal symptoms, such as stomach pain, bloating and nausea in pwCF.
3. Determining the best treatment (including which medication and when this should start) for non-tuberculous mycobacterium in pwCF.
4. Identifying which therapies are effective in delaying or preventing the progression of lung disease in the early life of pwCF.
5. Ways of preventing the development of CFRD in pwCF.
6. Assessing what technological advancements and effective ways of motivating, supporting pwCF can help improve and sustain adherence to their treatment.
7. Evaluating whether exercise could replace chest physiotherapy in the treatment of CF.
8. Establishing which antibiotic combinations and doses should be used during exacerbations in CF, and whether these should be rotated.
9. Exploring ways of reducing the negative effects of antibiotics including resistance and adverse symptoms in pwCF.
10. Exploring the best way of eradicating *Pseudomonas aeruginosa* in pwCF.