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# Continuous glucose monitoring systems for monitoring cystic fibrosis-related diabetes (Review)

Toner A, McCloy A, Dyce P, Nazareth D, Frost F

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[Intervention Review]

# Continuous glucose monitoring systems for monitoring cystic fibrosis-related diabetes

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## ABSTRACT

### Background

Cystic fibrosis (CF) is one of the most common life-shortening autosomal-recessive genetic conditions with around 100,000 people affected globally. CF mainly affects the respiratory system, but cystic fibrosis-related diabetes (CFRD) is a common extrapulmonary co-morbidity and causes excess morbidity and mortality in this population. Continuous glucose monitoring systems (CGMS) are a relatively new technology and, as yet, the impact of these on the monitoring and subsequent management of CFRD remains undetermined.

### Objectives

To establish the impact of insulin therapy guided by continuous glucose monitoring compared to insulin therapy guided by other forms of glucose data collection on the lives of people with CFRD.

### Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. Date of latest search: 23 September 2021.

We also searched the reference lists of relevant articles and reviews and online trials registries. Date of last search: 23 September 2021.

### Selection criteria

Randomised controlled studies comparing insulin regimens led by data from CGMS (including real-time or retrospective data, or both) with insulin regimens guided by abnormal blood glucose measurements collected through other means of glycaemic data collection in people with CFRD. Studies with a cross-over design, even with a washout period between intervention arms, are not eligible for inclusion due to the potential long-term impact of each of the interventions and the potential to compromise the outcomes of the second intervention.

### Data collection and analysis

No studies were included in the review, meaning that no data were available to be collected for analysis.

### Main results

Review authors screened 14 studies at the full-text stage against the review's inclusion criteria. Consequently, seven were excluded due to the study type being ineligible (not randomised), two studies were excluded due to their cross-over design, and two studies was excluded since the intervention used was not eligible and one was a literature review. One study in participants hospitalised for a pulmonary exacerbation is ongoing. Investigators are comparing insulin dosing via insulin pump with blood sugar monitoring by a CGMS

to conventional diabetes management with daily insulin injections (or on an insulin pump if already on an insulin pump in the outpatient setting) and capillary blood glucose monitoring. The participants in the control arm will wear a blinded continuous glucose monitoring system for outcome assessment.

In addition to this, one further study is still awaiting classification, and will be screened to determine whether it is eligible for inclusion, or is to be excluded, in an update of this review.

**Authors' conclusions**

No studies were included in the review, indicating that there is currently insufficient evidence to determine the impact of insulin therapy guided by CGMS compared to insulin therapy guided by other forms of glucose data collection on the lives of people with CFRD, nor on potential adverse effects of continuous glucose monitoring in this context. Randomised controlled studies are needed to generate evidence on the efficacy and safety of continuous glucose monitoring in people with CFRD. There is one relevant ongoing study that may be eligible for inclusion in a future update of this Cochrane Review, and whose results may help answer the review question.

## PLAIN LANGUAGE SUMMARY

**Continuous glucose monitoring systems for monitoring cystic fibrosis-related diabetes**

**Review question**

Canusing continuous glucose monitoring systems (CGMS) help people with cystic fibrosis-related diabetes (CFRD) manage their condition better?

**Background**

Cystic fibrosis (CF) is a life-shortening genetic condition. Many people with CF also develop CFRD, where their blood glucose, or the amount of sugar in their blood, can rise to harmful levels. People with CFRD seem to experience more frequent chest infections and a shorter life expectancy than people with CF who do not have diabetes.

CFRD can be managed with injections of insulin to help keep blood sugar in the normal range. To do this safely, people with CFRD need to routinely check blood sugar levels to make sure that they are taking the right amount of insulin. They usually do this by pricking their fingers and measuring a drop of blood on a machine. CGMS are devices that can be worn by a person and which closely estimate blood sugar levels without the need for regular pin-prick testing. They are a relatively new technology and we still do not know how they affect the monitoring and management of CFRD.

We wanted to find out whether using CGMS was better or worse than other methods, such as using the traditional 'finger stick' method, for monitoring blood sugar levels inpeople with CFRD. The main outcomes we wanted to look at were quality of life, any problems the CGMS might cause, and the amount of time a person's blood sugar stayed in the normal range. We decided that theseoutcomes were most important afterasking people with CFRD and their families what mattered most to them.

**Search date**

Evidence is current to: 23 September 2021.

**Study characteristics**

We did not find any relevant studies to include in the review, but we found two studies which we might be able to include in an update of this review when we have more information about them and they have both been completed.

**Key results**

When we ran our searches, we did not find any studies that matched our inclusion criteria. This means we cannot comment on how CGMS affects the outcomes we set out to investigate as there is no evidence for us to look at. We found one ongoing study in people with CFRD who are in hospital for a pulmonary exacerbation (flare up of chest symptoms). The study is comparing the effects of giving insulin via an insulin pump and monitoring blood sugar using a CGMS to giving daily insulin injections (or if participants are already using an insulin pump before being admitted to hospital, they continue with this) and monitoring blood sugar levels using the 'finger stick' method. The people using the finger stick method will wear a dummy CGMS so the clinicians measuring outcomes will not know which group they are in. The study has not yet been completed, so we could not include it, but we might be able to include it in a future version of this review.

More research is needed on this topic to help fill the gap in the evidence which we have identified in this review.

## BACKGROUND

Cystic Fibrosis (CF) is one of the most common life-shortening autosomal-recessive genetic conditions with around 100,000 people affected globally; one in 2500 newborns are affected by it within the UK and one in 25 people of northern European descent carry the gene (Ratjen 2003; Dodge 2007; Farrell 2018; UK Cystic Fibrosis Trust 2020). CF affects multiple systems, primarily the lungs; the main cause of mortality in people with the condition is respiratory failure (Cystic Fibrosis Foundation 2019). Other bodily systems are also affected, most notably the digestive and reproductive systems.

As survival in CF has improved dramatically over the last 50 years, cystic fibrosis related-diabetes (CFRD) has come to the forefront and is now one of the most common extrapulmonary co-morbidity in people with CF (pwCF) (Moran 2009). CFRD is associated with excess morbidity and mortality in pwCF and hence presents unique challenges for clinicians, patients and families alike.

### Description of the condition

The pathophysiology (the disordered processes within the body that are associated with a particular condition) of CFRD is complex and not fully understood. It is believed that CFRD results from a combination of chronic pancreatic inflammation and the loss of the islet cells, pancreatic duct obstruction leading to interstitial oedema, and ischaemic changes of the endocrine pancreas (Moran 1994; Hardin 1999; Marshall 2005; Hart 2018).

The improved life expectancy of pwCF means CFRD is a growing challenge to pwCF and clinicians, due in part to the fact that its prevalence is associated with increasing age with approximately 2% of children, 20% of adolescents and 50% of adults with CF thought to have the condition (Moran 2009); in addition, guidelines for screening have changed over the decades. Conversely, the advent of CFTR modulators and the improved clinical status of pwCF may have lowered the incidence of CFRD. The median age of onset of CFRD is 20 years (Finkelstein 1988; Lanng 1995; Yung 1999; Waugh 2012) and females are more susceptible, tending to develop CFRD at a younger age (Rosenecker 1995; Yung 1999; Waugh 2012). Unlike people with type 1 diabetes, people with CFRD (pwCFRD) do not develop a complete absence of insulin secretion, but retain some basal insulin secretion (Stutchfield 1988; Bridges 2018). However, few pwCF have truly normal glucose metabolism.

CFRD is associated with worse pulmonary function as well as malnutrition and liver dysfunction (Koch 2001; Marshall 2005). While not being associated with some of the classic macrovascular complications (affecting large blood vessels, including the coronary arteries and sizable arteries in the brain and limbs) seen in people with type 1 and type 2 diabetes, chronic complications of CFRD may include microvascular disease (disease of the finer blood vessels in the body, including the capillaries, as opposed to larger blood vessels). The presence of CFRD is also associated with an increase in early mortality of up to six-fold (Rodman 1986).

Given the major issue for pwCF is progressive lung failure (Cystic Fibrosis Foundation 2019), the most important impact of CFRD on morbidity and mortality is the hastened decline in lung function, associated with insulin deficiency and hyperglycaemia (Donaghue 2019). Inflammation of the airway epithelium, as 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 increased glucose concentration in the airway surface liquid lining the lung (Baker 2018). In some pwCFRD, a blood glucose level of 8 mmol/L and above has been linked to the detection of glucose in the airway surface liquid (Brennan 2007; Baker 2018). One of these studies showed an increase in the growth of organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* when airway surface liquid glucose concentration rose by just 0.5 mmol/L to 4.0 mmol/L, likely contributing to pwCFRD experiencing an increase in infection and decrease in lung function (Baker 2018). This could help explain why pwCFRD are more likely to experience reduced gas diffusion, require an increased effort to breathe and experience more lung stiffness and structural disease than pwCF who have normal glucose tolerance (Pitocco 2012; Widger 2013; Baker 2018). It is also likely that this pathology both contributes to, and is worsened by, an increased number of pulmonary exacerbations, inflammation of the airways, and bacterial colonisation (Marshall 2005; Limoli 2016). Appropriate insulin treatment is a vital component of managing CFRD as it both confers a short-term benefit, by lowering glucose levels, and long-term benefits of enhanced nutritional status and pulmonary function, on average delaying decline in $FEV_1$ by 34 months (Mohan 2008).

Insulinopenia (reduced insulin production or secretion) and hyperglycaemia have several early adverse effects on the lungs; one of the earliest manifestations of insulinopenia might also be weight loss. With damage occurring early when glucose levels are well below the threshold for the usual definition of diabetes by current criteria, there is a need to screen earlier and to start treating CFRD with as intensive an insulin regimen as possible. This makes effective glucose monitoring an important aspect of treatment.

### Description of the intervention

Subcutaneous insulin is the mainstay of CFRD treatment, and although a recent study found oral repaglinide to be as safe and as effective as insulin in controlling blood glucose (Ballmann 2014), oral diabetes medications (such as metformin and sulfonylureas) are not usually recommended (Moran 2010; New Zealand Ministry of Health 2014; Onady 2016; NICE 2017). The American Diabetes Association (ADA) recommends that people with insulin-dependent diabetes, including CFRD, track their glycaemic control using the traditional capillary blood glucose (CBG) 'finger stick' method at least three times daily (Moran 2010). Clinicians use these data to evaluate an individual's glycaemic trends and adjust insulin dosage or frequency accordingly.

While CGMS were developed to monitor glucose control in people with type 1 diabetes, these systems have recently emerged as a useful tool, validated in pwCF, to diagnose and monitor CFRD (Dobson 2004; Jefferies 2005; Moreau 2008; O'Riordan 2009; NICE 2017). CGMS record interstitial fluid glucose levels every five minutes, providing semi-continuous 24-hour information regarding glycaemic changes and trends through the day and night. Regular glucose readings over a period of days allow for the accumulation of substantially more data than intermittent CBG monitoring. CGMS transmit the blood glucose values calculated from interstitial fluid glucose concentrations to a display device or smartphone; the values are measured by a tiny subcutaneous filament sensor which is left in situ for at least 72 hours and for up to 10 days at a time. This process identifies abnormal glucose excursions more frequently than can be detected by CBG

'snapshots' alone (Tanenberg 2004). The use of the CGMS can be associated with skin-related issues, usually localised to the sensor insertion site, such as contact dermatitis, with other issues reported including minor bleeding, pain, and allergic reactions (Pleus 2019; ADA 2020). Some models of CGMS require the user to regularly calibrate the device, however, several newer devices no longer require this input.

There are two major types of CGMS, 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 real-time CGMS 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 CGMS). This form of CGMS has already been associated with improved quality of life (QoL) and treatment satisfaction in people with type 1 diabetes (Ang 2020).

'Blinded' or retrospective CGMS similarly allow more detailed data trends to be observed than CBG, but do not allow for the immediate modification of glucose levels as glucose levels are not displayed in real-time. These devices are worn for a period of time and the resulting data are used by clinicians and pwCFRD together to assess overall glycaemic trends (ADA 2020). Blinded CGMS have been shown to aid the monitoring and management of other forms of diabetes when used in conjunction with diabetes management education and insulin dose adjustment, but this has not yet been shown in CFRD (ADA 2020).

### How the intervention might work

Insulin therapy stabilises and improves lung function in pwCFRD (Mohan 2008). The data collected by CGMS may encompass both hyperglycaemic and hypoglycaemic episodes not identified by the pinpoint reading obtained by the CBG method. This may allow for more precise titration of insulin regimens, leading to better glycaemic control and therefore improved outcomes and QoL for pwCFRD. The accuracy of the devices themselves has also improved over time (Damiano 2014).

Typically pwCFRD require 0.5 to 0.8 units of insulin per kg per day (ISPAD 2018). Basal insulin is generally started at 0.125 units and titrated up to 0.25 units per kg per day. Meal coverage begins at 0.5 units per 15 g of carbohydrate consumed, this is then adjusted upwards by 0.5 unit increments until an individual's two-hour postprandial blood glucose is optimised (ISPAD 2018). This regimented treatment plan should be guided by at least three CBG readings per day, with additional readings before some activities, e.g. driving, vigorously exercising or when experiencing symptoms of hypoglycaemia (Moran 2010).

As there is already a high burden of treatment for pwCF (Davies 2020), reducing the frequency of CBG finger sticks may reduce the burden. It may also improve an individual's overall monitoring and control of their diabetes, especially for children or those who are needle-phobic.

Initiation of insulin treatment after consideration of CGMS data has also been associated with improved lung function and weight (Frost 2018).

### Why it is important to do this review

The impact of CGMS-guided insulin regimens on the lives of pwCFRD remains undetermined (O'Riordan 2009). This review intends to establish the impact of CGMS-guided insulin therapy on the lives pwCFRD in comparison to insulin therapy guided by other forms of glucose data collection.

Since CFRD is becoming more prevalent due to factors such as increased life expectancy of pwCF; the impact of CFRD is of increasing importance, as is research into reducing treatment burden (Sawicki 2013). It is imperative to ensure that new technologies are properly evaluated and information about their effectiveness is kept up to date so that the body of evidence supports the decision-making of policy makers, clinicians, and pwCFRD alike.

CGMS is expensive, particularly in comparison to measuring CBG (Niu 2016); and cost-effectiveness is an important consideration for policy makers. If, for example, monitoring CFRD with CGMS reduces morbidity, some cost savings may be made in preventing, rather than treating, complications; which are important considerations in large-scale public health issues. This review aims to assess whether there is sufficient evidence that it is appropriate and economically feasible to implement the widespread use of CGMS for managing CFRD.

## OBJECTIVES

To establish the impact of insulin therapy guided by continuous glucose monitoring compared to insulin therapy guided by other forms of glucose data collection on the lives of people with cystic fibrosis-related diabetes (pwCFRD).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs).

RCTs 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 the interventions and the potential to compromise the outcomes of the second intervention.

#### Types of participants

Eligible participants included pwCF of any age, who also had a diagnosis of CFRD. Diagnosis of CF must have been confirmed through either a sweat test or by genetic testing revealing two disease-causing variants. CFRD must have been diagnosed according to international diagnostic guidelines such as the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines which endorse diagnosis of CFRD during a period of stable baseline health according to the ADA guidelines (Moran 2010; ISPAD 2018):

- two-hour OGTT plasma glucose ≥ 11.1 mmol/L;
- fasting plasma glucose ≥ 7.0 mmol/L;
- random glucose ≥ 11.1mmol/L with symptoms;
- serial random glucose readings over 11 mmol/L.

As the sensitivity of HbA1c as a screening or diagnostic test for CFRD is controversial, participants with a normal HbA1c value were still to be included if they otherwise fulfilled the criteria for a formal CFRD diagnosis.

There were no specific exclusion criteria for pwCFRD for this review.

If we had identified any relevant studies containing mixed participant samples (e.g. people with type 1 diabetes and pwCFRD), the review authors aimed to discuss on a case-by-case basis whether to include these studies. If the consensus was that we should include any such study in the review, we would have contacted the relevant study authors to request the relevant specific subgroup data for pwCFRD for inclusion in the review. If the study authors had then been unable to provide the relevant data, we would not have included these studies in the meta-analysis.

### Types of interventions

We aimed to compare the effects of insulin regimens led by CGMS data (real-time or retrospective data, or both) as described above with the effects of insulin regimens guided by abnormal blood glucose measurements collected through other means of glycaemic data collection. This was to include, but not be limited to, standard practice, i.e. insulin regimen 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.

Both CBG and CGMS can be administered by either the individual or their carer.

*The ADA recommends that the CBG method is used at least three times daily to track glycaemic control; these data are recorded and used by clinicians to evaluate the glycaemic trends, allowing adjustment of insulin dosage or frequency.

### Types of outcome measures

We undertook stakeholder engagement in the form of semi-structured interviews with pwCFRD to ascertain which outcomes are most important to them and their carers. We formulated interview questions based on the combined clinical experiences of the review authors. This engagement process helped establish and appropriately order outcomes for this review and should improve the relevance of this review to consumers.

Outcome measures did not form part of the criteria for including or excluding studies in this review.

#### *Primary outcomes*

1. QoL (measured by a validated disease-specific tool, e.g. CFQ-QOL (Yohannes 2011))
2. Treatment-related adverse outcomes (e.g. hypoglycaemia (defined as ≤ 3.8 mmol/L), contact dermatitis, etc.)
3. Proportion of time within a normal* blood sugar profile (any range falling between 3.5 mmol/L to 8.0 mmol/L accepted) (Battelino 2019)

* There are no current official guidelines for 'time in range' values in pwCFRD, these are based on international consensus guidelines for pregnancy in other forms of diabetes due to the tighter glucose control required in pregnancy and the capacity for smaller glucose excursions in pwCFRD to cause problems as previously discussed (Battelino 2019; Chan 2019). Please note that a person's 'normal' range should be individualised to meet their needs and that therefore the 'normal' range can vary between individuals.

#### *Secondary outcomes*

1. Lung function
   a. $FEV_1$ % predicted (change from baseline or absolute post-treatment values)
   b. $FEV_1$ 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. Change in glycosylated haemoglobin A1c level (HbA1c)
5. Burden of treatment (as measured using a standardised scale, e.g. The TSQM questionnaire (Regnault 2012))
6. Self-efficacy** (as measured using a standardised scale, e.g. General Self Efficacy Scale (Jerusalem 1995))
7. Time off school or work (self-reported or otherwise documented)

** Self-efficacy for the purposes of this review was seen as the extent to which the individual can (or feels confident in their ability to) manage the monitoring and treatment of their medical condition independent from their carer or parent or medical staff, etc.

## Search methods for identification of studies

We searched for all relevant studies with no restrictions on language, year or publication status.

### Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a search of the Group's Cystic Fibrosis Trials Register for relevant studies using the following terms: (cystic fibrosis-related diabetes [CFRD] and impaired glucose tolerance [IGT]):kw.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of latest search: 23 September 2021.

We also searched the following databases and study registries:

- Embase Healthcare Databases Advanced Search (HDAS) (hdas.nice.org.uk/; 1974 to 11 Feb 2021);
- Web of Science Core Collection (www.webofknowledge.com; 1898 to 01 Feb 2021);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; 2000 to 18 Jan 2021);
- Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au; 1994 to 18 Jan 2021);

In our original protocol, we had published our intention to search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Toner 2020). Unfortunately, due to the ongoing COVID-19 pandemic, the authors were unable to access this database for the purposes of the review. We will endeavour to include a search of the WHO ICTRP in future updates of the review.

For details of our full search strategies, please see the appendices (Appendix 1).

### Searching other resources

If any studies had been included in the review, we would have checked their associated bibliographies for further references to relevant studies. We also included bibliographies for relevant systematic reviews in this process.

## Data collection and analysis

### Selection of studies

Two review authors (AT and AM) independently applied the predetermined selection criteria to identify potential studies to be included for review. We firstly screened the titles and abstracts of these articles, followed by screening of the full text of appropriate studies. Where we needed further information to determine eligibility or inclusion, we contacted the investigators for the necessary data. We resolved differences in opinion through discussion and referral to a third author was not necessary.

### Data extraction and management

If we include any studies in future updates of this review, two authors will independently extract data using a customised data extraction form. If disagreement on the suitability of a study or its risk of bias arises, we will resolve this through discussion or referral to a third author for consensus if necessary.

If we had identified any studies eligible for inclusion, we would have collated the following information for each study:

- administrative information including first author, year of publication, country, language;
- number of participants randomised and number of participants analysed, as well as participant characteristics, e.g. age, BMI, lung function;
- study characteristics including design of study, 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;
- data to address the primary and secondary outcome measures for this review;
- whether participants were using CGMS in conjunction with an insulin pump;
- source(s) of funding or other material support for the study;
- study authors' financial relationship and other potential conflicts of interest;
- dates when the study was conducted.

We would also have reported data within one of the following time-point groups in order to allow for variation in follow-up between studies:

- up to two weeks;
- over two weeks and up to one month;
- over one month and up to three months;
- over three months and up to six months;
- over six months and up to one year;
- annually thereafter.

### Assessment of risk of bias in included studies

Two review authors (AT and AM) would have independently assessed the risk of bias of included studies using the Cochrane tool and categorised these for several domains (listed below) as low risk of bias, high risk of bias or unclear risk of bias (Higgins 2017). We would have resolved any differences in opinion through discussion where possible, or through referral to a third author for consensus if necessary.

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other risk of bias.

We would then have included the results of these assessments in the review using a 'risk of bias' figure produced with RevMan (Review Manager 2014).

### Measures of treatment effect

#### *Dichotomous data*

If we include any studies in future updates of this review, we will calculate effect sizes as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcome data (e.g. number of people who experience adverse events).

#### *Continuous data*

As it is likely that authors of future studies included in updates of this review may use differing measurement scales, we plan to use calculated standardised mean differences (SMDs) with 95% CIs for continuous data (e.g. nutritional parameters). We will interpret SMDs as: under 0.2 = trivial effect; 0.2 to 0.5 = small effect; 0.5 to 0.8 = moderate effect; over 0.8 = large effect (Cohen 1988). If study authors report data using the same measurement scale, e.g. for amount of time off school or work, we plan to analyse the mean (standard deviation (SD) for each group and present the difference (MD) with corresponding 95% CIs.

***Time-to-event data***

We also plan to convert any time-to-event data into hazard ratios (HR) with 95% CIs (e.g. time until an adverse reaction is experienced).

**Unit of analysis issues**

Studies with a cross-over design, even with a washout period between intervention arms, are not eligible for inclusion due to the potential long-term impact of each the interventions and the potential to compromise the outcomes of the second intervention. Within RCTs, the unit of analysis is per individual. If we had identified any cluster-RCTs, we would have used the generic inverse-variance approach in RevMan to meta-analyse effect estimates and their standard errors (SE) from the subsequent analyses (Review Manager 2014).

**Dealing with missing data**

If we had identified any relevant studies where data were missing, we would have contacted the relevant authors to try and obtain the necessary data for inclusion in the review. If study authors had been unable to provide the relevant data, we would have made this clear in the review; and while we would still have included these studies in the review, we would not have pooled any data from them with other studies.

**Assessment of heterogeneity**

If we had included any studies in the review, we would have assessed for the presence and cause of both clinical heterogeneity and methodological heterogeneity. Firstly, by visually inspecting any forest plots we had been able to generate for inconsistency, or heterogeneity in size and direction of effect. Following on from this, we would have used the $I^2$ statistical test to estimate the level of heterogeneity present according to the following ranges.

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

**Assessment of reporting biases**

If we had a sufficient number of included studies, we would have created a funnel plot to help assess the risk of publication bias (Page 2021). Funnel plots can help to visualise the distribution of studies from the line of no effect, where 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 asymmetry could also be caused by selective reporting bias or heterogeneity.

**Data synthesis**

We would have performed a random-effects meta-analysis where studies had been sufficiently similar for the result to be clinically important. A random-effects meta-analysis allows studies to be weighted relatively more equally than by a fixed-effect analysis in the presence of heterogeneity (Deeks 2021). Due to the relatively new area of CGMS being used in CFRD, we felt this would provide a more accurate analysis than a fixed-effect analysis (which works best when there is minimal heterogeneity). In the case of a single study being eligible for inclusion in the review, we would also provide a narrative description of the single study's results.

**Subgroup analysis and investigation of heterogeneity**

We would have carried out the statistical analysis using RevMan according to the statistical guidelines referenced in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2021; Review Manager 2014).

As CFRD is more common in adults, we did not plan to consider subgroup analysis by age which could have introduced bias, e.g. older pwCF might have different perceived benefits. However, if, when we analysed results, it had become apparent that there was substantial heterogeneity between studies (identified through $I^2$ values as detailed above), we had planned to conduct the following subgroup analyses:

- blinded versus non-blinded* CGMS;
- older versions of CGMS versus newer versions;
- CGMS with an insulin pump versus CGMS alone;
- intermittently scanned CGMS versus continuously scanned CGMS.

* non-blinded CGMS encompasses both intermittently scanned CGMS and continuously scanned CGMS

**Sensitivity analysis**

If we had included one or more studies with a high risk of bias in one or more domains (e.g. random sequence generation or allocation concealment), we would have performed a sensitivity analysis excluding these studies, performing another meta-analysis with the new data set and comparing any impact on the results from these potential biases.

**Summary of findings and assessment of the certainty of the evidence**

If we had been able to include any studies, we would have produced summary of findings tables for each comparison, showing the type of population and the setting in which they have been investigated and the illustrative risk of the outcomes measured (Review Manager 2014). We have included a template for these tables in the appendices (Appendix 2). Within each table we would have reported results for the following outcomes at six months, due to the long-term impact of glycaemic control and low insulin secretion as outlined above (Description of the condition).

- QoL (we would have compared validated tools in a like for like manner, e.g. we would consider CFQ-R Adult and CFQ-R Teen separately)
- Treatment-related adverse events
- Proportion of time within a normal blood sugar profile (we would have accepted any range falling between 3.5 mmol/L to 8.0 mmol/L)
- $FEV_1$ % predicted (change from baseline)
- BMI percentile (change from baseline)
- CFRD-related adverse outcomes

We would have used the GRADE approach to assess the certainty of the body of evidence from each study, and then presented this within the summary of findings tables (Atkins 2004). The

levels of confidence that the true effect of the intervention lie close to the estimate of the effect within the GRADE framework are; high certainty, moderate certainty, low certainty or very low certainty. RCTs start with a high certainty that the true effect of the intervention lies close to the estimate of the effect and we would downgrade as appropriate after assessing the risk of bias, imprecision, indirectness and inconsistency. We would have then reported the final level in the summary of findings table(s).

# RESULTS

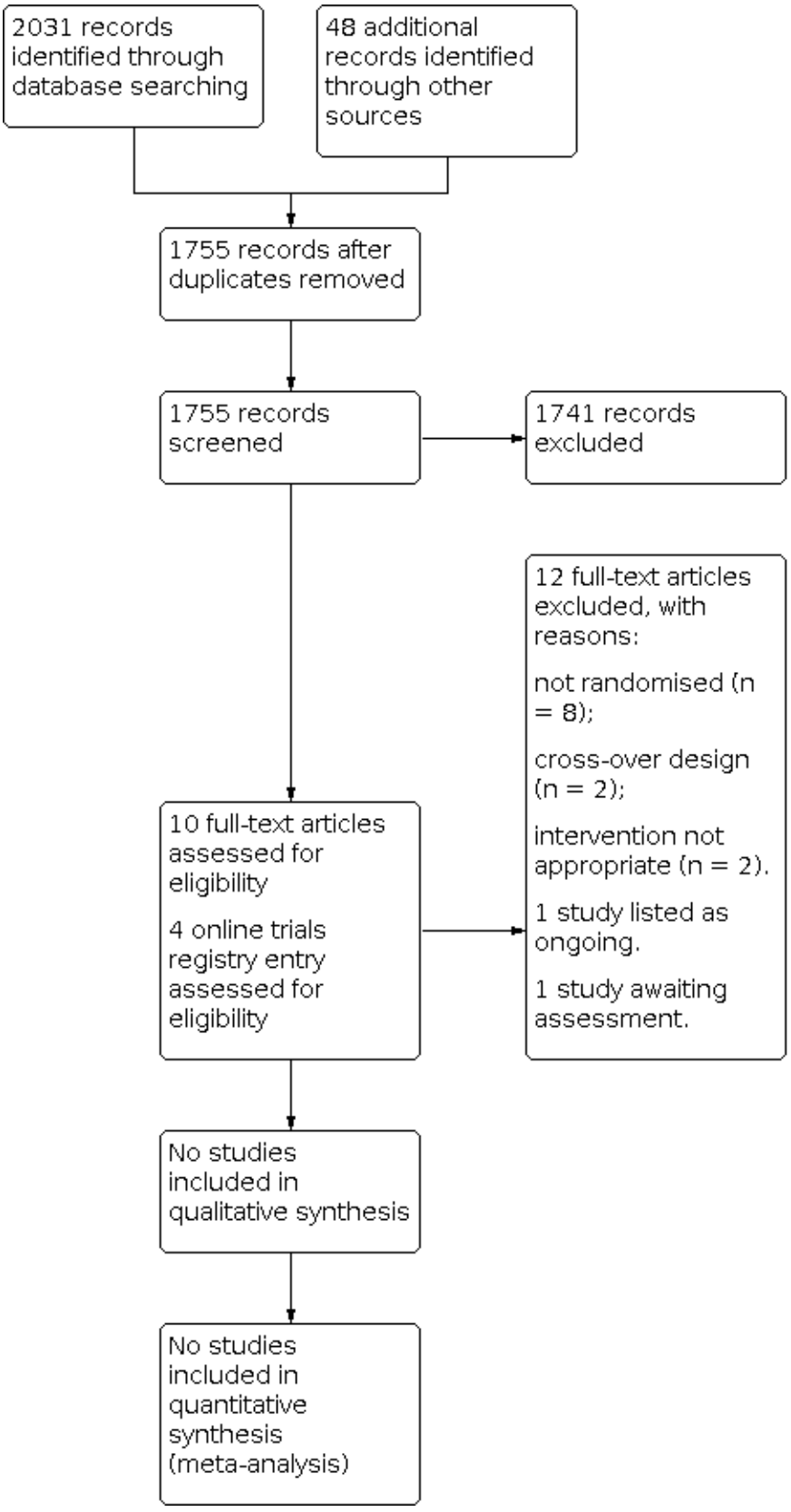
## Description of studies

Please see the tables for further details (Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies).

### Results of the search

The electronic searches initially generated 2079 results, from which we removed 324. From the remaining 1755 titles, we considered 10papers and fourtrials registry entries to be potentially eligible after preliminary screening. After full-text screening of the final eight papers against the inclusion criteria determined that there were no studies eligible for inclusion in the review; one study is ongoing. Five studies are awaiting assessment in an update of this review (Figure 1).

**Figure 1. Study flow diagram.**



### Included studies

No studies were included in the review.

### Excluded studies

From our searches, we assessed 12 full texts of studies for inclusion. One of these was excluded as it was a literature review (Jones 2016). We excluded two trials due to their cross-over design (Sherwood 2020; Stackhouse 2017). Three further papers referred to retrospective observational studies, and thus were not eligible for inclusion in the review (Guilbert 2018; Hagan 2020; Jackson 2017). Another two papers were not related to insulin treatment (EUCTR2004-005019-28-GB; O'Riordan 2009). The remaining four studies were not randomised (NCT04533646; Rahman 2020; Shimmin 2020; Tomlinson 2021).

Please see the 'Characteristics of excluded studies' table for further information.

#### *Studies awaiting classification*

One study looking at the feasibility of outpatient closed loop control with the iLet bionic pancreas in people with CFRD is currently still recruiting participants and is listed as awaiting classification (NCT03258853).

##### Design

The 14-day study is open-label and has a randomised cross-over design; it is being run at a single centre in the USA (Massachusetts General Hospital) in collaboration with Beta Bionics, Inc.

##### Participants

Investigators are aiming to recruit 60 participants aged 10 years and over who have been diagnosed with CFRD. Participants will be managing their insulin requirements either by insulin pump or daily injections and have a minimum insulin requirement of at least 0.1 unit/kg/day. A wide range of insulin requirrements will be included.

##### Interventions

Participants in the intervention arm will wear a bionic pancreas system that automatically delivers insulin using a CGM device for 14 days. The system uses CGM as input to the controller. Participants in the control group will manage their CFRD using standard of care as per their typical regimen (including use of an insulin pump or injectable insulin) for 14 days, and will wear a blinded CGM device throughout the study period.

##### Outcome measures

The primary outcome measure is the amount of time with CGM glucose values between 70 and 180 mg/dl. Secondary outcome measures include the amount of time spent with other CGM glucose levels (under 54 mg/dl, under 70 mg/dl, over 180 mg/dl and over 250 mg/dl), number of episodes of hypoglycaemia, number of participants who achieve the ADA goal for therapy (a mean CGM glucose below 154 mg/dl), the average CGM glucose level, the number of participants who have less than 1% of CGM glucose values below 54 mg/dl, the number of participants who have less than 1% of CGM glucose values below 54 mg/dl and also have a mean CGM glucose level of 154 mg/dl or lower, and finally the number of participants who have at least 70% of their CGM glucose values between 70 and 180 mg/dl.

#### *Ongoing studies*

Our search identified one protocol for a randomised, parallel-assignment, open-label study which has not yet been undertaken but may be eligible for inclusion in a future update of this review (NCT03939065). This study "Sensor Augmented Pump (SAP) Therapy for Inpatient CFRD Management" aims to recruit 36 participants between 8 and 25 years of age who have CFRD and who have been admitted to the Children's Hospital in Colorado during a pulmonary exacerbation episode. The study will compare the use of CGM and an insulin pump with 'standard care', i.e. CBG. The participants in the 'standard care' arm will also wear a blinded CGM for outcome assessment, and all participants will be followed up for three weeks.

The primary outcome for the study is the difference between groups in CGM amount of time over 140 mg/dL at up to three weeks. Secondary outcomes include: the change in $FEV_1$ (% and L) at one week; the change in circulatory markers of inflammation (hsCRP and calprotectin) at one week; the change in weight change at one week; and CBG (mg/dL) at three weeks. The study is listed as having begun on 12 June 2020 and is due to be completed in February 2023 (NCT03939065).

## Risk of bias in included studies

No studies were included in the review.

## Effects of interventions

No studies were included in the review, therefore no data or narrative information on the effects of the interventions could be presented.

# DISCUSSION

No studies were included in the review, indicating that there is currently insufficient evidence to determine the impact of insulin therapy guided by CGM compared to insulin therapy guided by other forms of glucose data collection on the lives of people with CFRD.

## Summary of main results

There were no RCTs found, which met the criteria for inclusion in the review. The review authors screened eight studies at the full-text stage, none of which were found to be eligible; one was a literature review (Jones 2016), two further papers were retrospective observational studies (Jackson 2017; Guilbert 2018), two studies were not randomised (Rahman 2020; Shimmin 2020), one was a cohort study not related to insulin treatment (O'Riordan 2009) and we excluded the final two studies due to their cross-over design (Stackhouse 2017; Sherwood 2020). It is noted that one ongoing RCT was identified which may be eligible for inclusion in a future update of this Cochrane Review (NCT03939065). The parallel RCT is comparing the use of insulin dosing via insulin pump titrated according to a CGMS, to conventional diabetes management with daily insulin injections (or insulin pump if this is the participant's usual care) according to capillary blood glucose monitoring. Participants in the latter group wear a blinded CGMS for outcome assessment (NCT03939065). Further details of the study are included under 'Characteristics of ongoing studies'. Five studies are awaiting assessment in an update of this review pending further information (EUCTR2004-005019-28-GBa; Hagan

2020a; NCT03258853; NCT04533646a; Tomlinson 2021a). Details about these studies are provided in the characteristics tables above; one of these is a retrospective observational study, two appear to be randomised controlled trials, and a further two studies do not have significant information available about randomisation/methods.

### Overall completeness and applicability of evidence

No studies were included in the review, hence there is no evidence to assess.

### Quality of the evidence

No studies were included in the review, hence there is no evidence to assess.

### Potential biases in the review process

This work represents an extensive review of the Cystic Fibrosis and Genetic Disorders Review Group's CF Trials Register and multiple online trials databases. Two authors independently screened the results against the eligibility criteria for inclusion which were published in a peer-reviewed protocol (Toner 2020).

It is recognised that, due to the advent of the COVID-19 pandemic, the WHO ICTRP was inaccessible for data searching. 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 the review, meaning it is unlikely that any relevant studies will have been missed. For future versions of the review, the authors will endeavour to conduct and include a search of the WHO ICTRP as stipulated in the original protocol (Toner 2020).

### Agreements and disagreements with other studies or reviews

As far as the authors are aware, this is the first published systematic review to examine this topic. However, several international guidelines comment on the use of CGMS in the context of CFRD, including "Clinical care guidelines for cystic fibrosis–related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society" (Moran 2010) as well as "Clinical practice consensus guidelines 2018: management of cystic fibrosis-related diabetes in children and adolescents", produced by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (ISPAD 2018). Further details of the stance taken in these guidelines are included below (Implications for practice).

## AUTHORS' CONCLUSIONS

### Implications for practice

We found no randomised controlled trials (RCTs) meeting the criteria for inclusion in the review. As a result, it is not currently possible to draw reliable conclusions about the impact on the lives of people with cystic fibrosis-related diabetes (CFRD) of insulin therapy guided by continuous glucose monitoring systems (CGMS) compared to insulin therapy guided by other forms of glucose data collection.

However, we note that the current position taken in the guideline published by the International Society for Pediatric and Adolescent Diabetes (ISPAD) is that "CGM should be considered a useful tool for insulin dosage adjustment and to alert the patient to hypoglycemia" (ISPAD 2018). This is echoed by guidance from the American Diabetes Association, as endorsed by the Cystic Fibrosis Foundation, which states that CGMS "may be useful for clinical management in some patients [with CFRD]" (Moran 2010).

### Implications for research

This review found a paucity of evidence regarding the impact of insulin therapy guided by CGMS compared to insulin therapy guided by other forms of glucose data collection on the lives of people with CFRD. 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.

This gap in the evidence would be best addressed by large and robust RCTs including people with a formal diagnosis of CFRD. It would also be ideal for any RCT 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. Such studies could focus on the impact of using data collected via CGMS to make adjustments to an individual's CFRD treatment, such as insulin dosage or frequency. Alternatively, a future study could attempt to assess whether manipulating the diet of people with CFRD could prevent the significant peaks and troughs in glucose levels that are often picked up via CGMS data collection.

Previous studies of CGMS technology in other types of diabetes have demonstrated the potential for variability in effect across populations with diabetes (Langendam 2012), highlighting the need for future research to investigate the impact of CGMS on different demographics within the CFRD population, i.e. across different age groups and during pregnancy. Ideally, studies would take into account similar insulin regimens including insulin type, dose and mode of delivery (i.e. pump versus multiple daily injections), as well as similar CGMS models. This would reduce bias by allowing greater homogenisation of the study population. A cost-benefit analysis of differing CGMS models and insulin regimens in the context of CFRD could also produce important data to inform the decision-making of stakeholders.

Researchers may encounter difficulties when conducting RCTs in this area, including the inability to completely mask participants and study personnel from the intervention allocated to a particular group. For example, any person using CGMS has sensors inserted into the skin and readings are taken such that the wearer is aware of the functionality of the device and a placebo device would not be effective. This is a recognised issue with glucose technology studies to which there is no practical solution (Bolinder 2016; Maahs 2016). The potential for an increased risk of bias associated with this problem should therefore 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 study taken into account.

In recent years it has been suggested that cystic fibrosis transmembrane conductance regulator (CFTR) modulators may have a favourable effect on insulin secretion in people with CFRD

(Gaines 2021; Mehfooz 2019; Volkova 2020). These interventions may impact the management of CFRD in the future, although a current lack of conclusive evidence necessitates further research in this area before any conclusions can be drawn.

In future versions of this review, it may be appropriate to include cross-over studies where only data from the first intervention period would be included in the analysis, to allow the impact of any such data to be assessed.

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Rosenecker J, Eichler I, Kühn L, Harms HK, von der Hardt H. Genetic determination of diabetes mellitus in patients with cystic fibrosis. Multicenter Cystic Fibrosis Study Group. *Journal of Pediatrics* 1995;**127**(3):441-3.

**Sawicki 2013**

Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL, et al. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *Journal of Cystic Fibrosis* 2013;**12**(5):461-7. [DOI: 10.1016/j.jcf.2012.12.009]

## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

**Stutchfield 1988**

Stutchfield PR, O'Halloran SM, Smith CS, Woodrow JC, Bottazzo GF, Heaf D. HLA type, islet cell antibodies, and glucose intolerance in cystic fibrosis. *Archives of Disease in Childhood* 1988;**63**(10):1234-9.

**Tanenberg 2004**

Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, et al. Use of the continuous glucose monitoring system to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. *Mayo Clinic Proceedings* 2004;**79**(12):1521-6.

**UK Cystic Fibrosis Trust 2020**

UK Cystic Fibrosis Trust. Cystic Fibrosis FAQs. www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs# (accessed 05 October 2020).

**Volkova 2020**

Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *Journal of Cystic Fibrosis* 2020;**19**(1):68-79. [DOI: 10.1016/j.jcf.2019.05.015]

**Waugh 2012**

Waugh N, Royle P, Craigie I, Ho V, Pandit L, Ewings P, et al. Screening for cystic fibrosis-related diabetes: a systematic review. *Health Technology Assessment* 2012;**16**(24):iii-iv, 1-179.

**Widger 2013**

Widger J, Ranganathan S, Robinson PJ. Progression of structural lung disease on CT scans in children with cystic fibrosis related diabetes. *Journal of Cystic Fibrosis* 2013;**12**(3):216-21.

**Yohannes 2011**

Yohannes AM, Dodd M, Morris J, Webb K. Reliability and validity of a single item measure of quality of life scale for adult patients with cystic fibrosis. *Health Quality of Life Outcomes* 2011;**9**:105.

**Yung 1999**

Yung B, Kemp M, Hooper J, Hodson ME. Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. *Thorax* 1999;**54**(1):40-3.

### References to other published versions of this review

**Toner 2020**

Toner A, McCloy A, Dyce P, Nazareth D, Frost F. Continuous glucose monitoring systems for monitoring cystic fibrosis-related diabetes.. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No: CD013755. [DOI: 10.1002/14651858.CD013755]

| Study | Reason for exclusion |
|---|---|
| EUCTR2004-005019-28-GB | Intervention not related to insulin treatment. |
| Guilbert 2018 | Study type not eligible (non-randomised study). |
| Hagan 2020 | Study type not eligible (non-randomised study). |
| Jackson 2017 | Study type not eligible (non-randomised study). |
| Jones 2016 | Study type not eligible (literature review). |
| NCT04533646 | Study type not eligible (non-randomised study). |
| O'Riordan 2009 | Intervention not related to insulin treatment. |
| Rahman 2020 | Study type not eligible (non-randomised study). |
| Sherwood 2020 | Study type not eligible (cross-over study). |
| Shimmin 2020 | Study type not eligible (non-randomised study). |
| Stackhouse 2017 | Study type not eligible (cross-over study). |
| Tomlinson 2021 | Study type not eligible (non-randomised study). |

## Characteristics of studies awaiting classification *[ordered by study ID]*

### NCT03258853

| | |
|---|---|
| Methods | Interventional clinical trial.<br>Design: randomised cross-over assignment (open-label).<br>Duration: 14-days.<br>Location: single cente in USA (Massachusetts General Hospital). |
| Participants | 60 participants.<br>**Inclusion criteria**<br>1. Age >/= 10 years and have had a diagnosis of CFRD managed using either an insulin pump or multiple daily injections.<br>2. Mean CGM glucose >/=125 mg/dl as determined by the participant's personal CGM 30-day download if CGM is used as part of their usual care. If the participant does not use CGM, haemoglobin A1c >/= 6% within the last 6-months from available medical records will be required.<br>3. Minimum insulin requirement of >/=0.1u/kg/day. To ensure that participants with a wide range of insulin requirements are included, participants whose insulin requirement is below 0.3 u/kg/day will be limited to approximately 1/3 of the enrolled >/=18 year old adult cohort.<br>4. Willing to wear iLet infusion sets and one Dexcom CGM sensor and change sets at least every other day in the iLet arm.<br>5. Assent obtained for participants under 18 years of age.<br>**Exclusion criteria**<br>1. Diabetes from etiologies other than CFRD.<br>2. Unable to provide informed consent (e.g. impaired cognition or judgment). |

**NCT03258853** *(Continued)*

3. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory, unable to speak and read English).
4. Current participation in another clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the participant.
5. Pregnancy (positive urine human chorionic gonadotropin), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception.
6. History of hypoglycaemic seizures (grand-mal) or coma in the last year.
7. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation. Unable to avoid hydroxyurea for duration of study (interferes with accuracy of Dexcom G6 CGM).
8. Unable to avoid taking higher than the maximum dose of acetaminophen from all sources for the duration of the study (interferes with accuracy of Dexcom G6 CGM)
9. Have started or stopped a CFTR modulator in the past 4 weeks.
10. Established history of allergy or severe reaction to adhesive or tape that must be used in the study.
11. History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight.
12. Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) or non-insulin injectable (GLP-1 agonists, amylin) anti-diabetic medications.
13. History of lung or liver transplant or anticipated lung transplant (on transplant list).
14. No acute pulmonary exacerbation or hospitalizations within the past 4 weeks or treatment with IV antibiotics in the past 4 weeks.
15. Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study.
16. History of severe liver disease, including cirrhosis or portal hypertension.
17. Presence of a medical condition or use of a medication that, in the judgment of the investigator, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following:
    a. current alcohol abuse (intake averaging more than 3 drinks daily in last 30 days) or other substance abuse (use within the last 6 months of controlled substances other than marijuana without a prescription);
    b. unwilling or unable to refrain from drinking more than 2 drinks in an hour or more than 4 drinks in a day during the trial;
    c. unwilling or unable or to avoid use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study (use of beta blockers will be allowed as long as the dose is stable and the participant does not meet the criteria for hypoglycaemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator);
    d. renal failure requiring dialysis;
    e. any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion);
    f. congestive heart failure (established history of CHF, lower extremity edema, paroxysmal nocturnal dyspnea, or orthopnea);
    g. history of transient ischaemic attack or stroke;
    h. seizure disorder, history of any non-hypoglycaemic seizure within the last 2 years, or ongoing treatment with anticonvulsants;
    i. history of intentional, inappropriate administration of insulin leading to severe hypoglycaemia requiring treatment.

| | |
|---|---|
| Interventions | **Experimental arm: bionic pancreas system**<br><br>Participants in this arm will wear a bionic pancreas system that automatically delivers insulin using a CGM device for 14 days. The system uses CGM as input to the controller. |

**NCT03258853** *(Continued)*

| | |
|---|---|
| | **Control arm: standard of care and CBG (with blinded CGM)**<br><br>Participants in this arm will manage their diabetes using standard of care for diabetes as per their typical regimen including use of an insulin pump or injectable insulin for 14 days, and will wear a CGM device throughout the study period. |
| Outcomes | **Primary outcome measures**<br><br>1. % time spent with CGM glucose values between 70 and 180 mg/dl<br><br>**Secondary outcome measures**<br><br>1. % time spent with CGM glucose: < 54 mg/dl, < 70 mg/dl, > 180 mg/dl, >250 mg/dl<br>2. Number of episodes participants reported experiencing symptoms of low blood sugar (hypoglycaemia)<br>3. Number of participants who achieve a mean CGM glucose < 154 mg/dl, which is the estimated average glucose for a hemoglobin A1c of 7% (ADA goal for therapy)<br>4. Average CGM glucose<br>5. Number of participants who have less than 1% of CGM glucose values < 54 mg/dl<br>6. Number of participants who have less than 1% of CGM glucose values < 54 mg/dl and also have a mean CGM glucose that is less than or equal to 154 mg/dl<br>7. Number of participants who have 70% or more of their CGM glucose values between 70 and 180 mg/d |
| Notes | Full title: Feasibility of Outpatient Closed Loop Control With the iLet Bionic Pancreas in Cystic Fibrosis Related Diabetes |

CBG; capiliary blood glucose
CF: cystic fibrosis
CFRD: cystic fibrosis-related diabetes
CGM: continuous glucose monitoring

## Characteristics of ongoing studies *[ordered by study ID]*

**NCT03939065**

| | |
|---|---|
| Study name | Sensor Augmented Pump (SAP) Therapy for Inpatient CFRD Management |
| Methods | Interventional clinical trial<br><br>Design: randomised parallel assignment, open-label<br><br>Duration: 3-week follow-up period<br><br>Location: Children's Hospital Colorado, University of Colorado Denver |
| Participants | 36 participants.<br><br>Inclusion Criteria:<br><br>1. Age ≥8 years to 25 years<br>2. Confirmed diagnosis of CF by consensus guidelines<br>3. Diagnosis of CFRD based on American Diabetes Association and CFF criteria<br>4. Admission for pulmonary exacerbation<br><br>Exclusion Criteria:<br><br>1. Known type 1 or type 2 diabetes, monogenic diabetes |

| | |
|---|---|
| **NCT03939065** *(Continued)* | 2. Critical illness requiring admission to the intensive care unit<br>3. Admission for indications other than pulmonary exacerbation (ex. Distal intestinal obstructive syndrome, surgery)<br>4. Pregnancy |
| Interventions | **Experimental arm: insulin pump and CGM**<br>Participants in this arm will receive their insulin dosing via insulin pump and their blood sugars will be monitored using CGM.<br>**Control arm: standard of care and CBG (with blinded CGM)**<br>Participants in this arm will receive conventional diabetes management with daily insulin injections (or on an insulin pump if already on an insulin pump in the outpatient setting) and capillary blood glucose monitoring. These participants will also wear a blinded CGM for outcome assessment. |
| Outcomes | **Primary outcome measures**<br>1. Differences in percent time >140 mg/dl on CGM between groups at up to 3 weeks<br>**Secondary outcome measures**<br>1. Change in FEV1 (% and L) at 1 week<br>2. Change in circulatory markers of inflammation (hsCRP and calprotectin) at 1 week<br>3. Change in weight change at 1 week<br>4. Statstrip glucose (glucose obtained from bedside glucometer (mg/dl)) at 3 weeks<br>**Other outcome measures**<br>1. Beta-cell function (measures derived from oral glucose tolerance testing, including insulin and c-peptide area under the curve) within 24 hours of admission |
| Starting date | 12 June 2020 |
| Contact information | Contact: Eileen Findlay (eileen.findlay@childrenscolorado.org)<br>Contact: Christine Chan, MD (christinel.chan@childrenscolorado.org) |
| Notes | Estimated completion date: February 2023 |

CGM: continuous glucose monitoring
hsCRP: high-sensitivity C-reactive protein
FEV1: forced expiratory volume in 1 second
SAP: sensor augmented pump
RCT: randomised controlled trial

## APPENDICES

### Appendix 1. Search Methods - Electronic Searches

| Database or resource | Strategy | Date searched |
|---|---|---|

*(Continued)*

| | | |
|---|---|---|
| Embase Healthcare Databases Advanced Search (HDAS) (hdas.nice.org.uk/database-info) | #1 (cystic fibrosis).ti,ab,if,sh<br>#2 (mucoviscidos*).ti,ab,if,sh<br>#3 cystic* ADJ10 (fibro*).ti,ab,if,sh<br>#4 fibrocyst* ADJ10 (pancrea).ti,ab,if,sh<br>#5 "CYSTIC FIBROSIS"/<br>#6 (1 OR 2 OR 3 OR 4 OR 5)<br>#7 diabetes OR glucose OR insulin OR sugar OR (CFRD).ti,ab,if,sh<br>#8 exp "DIABETES MELLITUS"/<br>#9 (7 OR 8)<br>#10 (6 AND 9)<br>#11 (guide OR guided OR test* OR monitor OR monitoring OR manage OR management OR led OR CGMS).ti,ab,if<br>#12 (10 AND 11)<br>#13 "RANDOMIZED CONTROLLED TRIAL"/<br>#14"CONTROLLED CLINICAL TRIAL"/<br>#15 (random*).ti,ab<br>#16 RANDOMIZATION/<br>#17 "INTERMETHOD COMPARISON"/<br>#18 (placebo).ti,ab<br>#19 compare OR compared OR (comparison).ti<br>#20 (evaluated OR evaluate OR evaluating OR assessed OR assess) AND (compare OR compared OR comparing OR comparison).ab<br>#21 open ADJ (label).ti,ab<br>#22 (double OR single OR doubly OR singly) ADJ (blind OR blinded OR blindly).ti,ab<br>#23 "DOUBLE BLIND PROCEDURE"/<br>#24 (parallel group*1).ti,ab<br>#25 crossover OR (cross over).ti,ab<br>#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<br>#27 assigned OR (allocated).ti,ab<br>#28 controlled ADJ7 (study OR design OR trial).ti,ab<br>#29 volunteer OR (volunteers).ti,ab<br>#30 "HUMAN EXPERIMENT"/<br>#31 (trial).ti | 11 Feb 2021 |

(Continued)

| | | |
|---|---|---|
| | #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)<br><br>#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)<br><br>#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)<br><br>#35 ((case ADJ control*) AND random*) NOT (randomi?ed controlled).ti,ab<br><br>#36 Systematic review NOT (trial OR study).ti<br><br>#37 nonrandom* NOT (random*).ti,ab<br><br>#38 ("Random field*").ti,ab<br><br>#39 random cluster ADJ3 (sampl*).ti,ab<br><br>#40 ((review).ab AND (review).pt) NOT (trial).ti<br><br>#41 ("we searched").ab AND ((review).ti OR (review).pt)<br><br>#42 ("update review").ab<br><br>#43 databases ADJ4 (searched).ab<br><br>#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"/<br><br>#45 "ANIMAL EXPERIMENT"/ NOT ("HUMAN EXPERIMENT"/ OR "HUMAN"/)<br><br>#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)<br><br>#47 32 NOT 46<br><br>#48 (12 AND 47)<br><br>NOTE: Lines #13-#47 are the "records with publication type RCT" filter available from: https://www.cochranelibrary.com/central/central-creation | |
| Web of Science Core Collection<br><br>(Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC) (www.webofknowledge.com/WOS) | [Advanced Search]<br><br>#1 TS=(cystic fibrosis)<br>#2 TS=(mucoviscidos*)<br>#3 TS=(cystic* NEAR/10 fibro*)<br>#4 TS=(fibrocyst* NEAR/10 pancrea*)<br>#5 #4 OR #3 OR #2 OR #1<br>#6 TS=(diabetes OR glucose OR insulin OR sugar OR CFRD OR CRD**)<br>#7 #6 AND #5<br>#8 TS=(guide OR guided OR test* OR monitor* OR manage OR management OR led OR CGMS OR CGM)<br>#9 #8 AND #7<br>#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* OR match*)<br>#11 #10 AND #9 | 01 Feb 2021 |
| Clinicaltrials.gov | [Advanced Search] | 18 Jan 2021 |

*(Continued)*

| | | |
|---|---|---|
| (clinicaltrials.gov/) | CONDITION/ DISEASE: Cystic Fibrosis Diabetes OR cfrd<br>OTHER TERMS: guide OR guided OR test OR testing OR monitor OR monitored OR monitoring OR manage OR management OR CGMS OR led OR adjust OR adjusted OR modify OR modified<br>STUDY TYPE: Interventional Studies | |
| Australian New Zealand Clinical Trials Registry (ANZCTR)<br>(www.anzctr.org.au/) | [Advanced Search Form]<br>REGISTRY: ANZCTR<br>HEALTH CONDITION(S) OR PROBLEM(S) STUDIED: diabetes<br>CONDITION CATEGORY: Human Genetics and Inherited Disorders<br>CONDITION CODE: cystic fibrosis | 18 Jan 2021 |
| WHO ICTRP<br>(www.who.int/ictrp/search/en/) | [Advanced Search Form]<br>TITLE: diabetes OR CFRD OR CFD<br>and<br>CONDITION: cystic fibrosis<br>RECRUITMENT STATUS: All | Unable to search, last attempted 31/03/2021 |

## Appendix 2. Blank summary of findings table

**Intervention A compared with placebo or intervention B for cystic fibrosis-related diabetes**

**Patient or population**: people with cystic fibrosis-related diabetes

**Settings**: inpatients or outpatients

**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**<br>Scale: units<br>Follow-up: at 6 months | | | | | | |
| **Treatment-related adverse events**<br>Scale: complete units to be used | | | | | | e.g. hypoglycaemia |

*(Continued)*

| | |
|---|---|
| Follow-up: at 6 months | (defined as ≤ 3.8 mmol/L), contact dermatitis etc. |
| **Proportion of time within a normal blood sugar profile** (any range falling between 3.5 mmol/L to 8.0 mmol/L accepted)<br><br>Follow-up: at 6 months | |
| **$FEV_1$ % predicted**<br><br>(change from baseline)<br><br>Follow-up: at 6 months | |
| **BMI percentile** (change from baseline)<br><br>Follow-up: at 6 months | |
| **CFRD-related adverse outcomes**<br><br>Follow-up: at 6 months | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Abbreviations**: **BMI**: body mass index; **CBG**: capillary blood glucose; **CGMS**: continuous glucose monitoring systems; **CI**: confidence interval; **$FEV_1$**: forced expiratory volume in 1 second.

GRADE Working Group grades of evidence
**High quality**: further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality**: we are very uncertain about the estimate.

## HISTORY

Protocol first published: Issue 10, 2020

## CONTRIBUTIONS OF AUTHORS

| TASK | WHO UNDERTOOK THE TASK? |
|---|---|
| Conceiving the review | AT |
| Designing the review | AT, DN, FF |
| Coordinating the review | AT |
| Data collection for the review | AT, AM |

| | |
|---|---|
| Designing search strategies | AT, DN, FF, Natalie Hall (Information Specialist) |
| Undertaking searches | AT, Natalie Hall (Information Specialist) |
| Screening search results | AT, AM |
| Screening retrieved papers against eligibility criteria | AT, AM |
| Appraising quality of papers | AT, AM |
| Extracting data from papers | AT, AM |
| Writing to authors of papers for additional information | AT |
| Obtaining and screening data on unpublished studies | AT |
| Data management for the review | AT, DN |
| Entering data into RevMan | AT |
| Analysis of data | AT, DN, FF |
| Interpretation of data | AT, DN, FF |
| Providing a methodological perspective | DN, FF |
| Providing a clinical perspective | DN, FF, PD |
| Providing a policy perspective | DN, FF |
| Writing the review (or protocol) | AT, DN |
| Providing general advice on the review | DN, FF |
| Guarantor of the review | AT |

## DECLARATIONS OF INTEREST

All authors: none known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support provided

### External sources

- National Institute for Health Research, UK

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our original protocol we stated our intention to search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Toner 2020). Unfortunately, due to the ongoing COVID-19 pandemic, the WHO ICTRP was inaccessible for data searching. However,

the Cochrane CENTRAL clinical trials registry, which is regularly updated with relevant records for randomised controlled trials (RCTs) or quasi-RCTs listed in the ICTRP, was searched for the purposes of the review, meaning it is unlikely that any relevant studies will have been missed. For future versions of the review, the authors will endeavour to conduct and include a search of the WHO ICTRP as stipulated in the original protocol (Toner 2020).

Additionally, our search strategy for clinicaltrials.gov has been updated to remove the truncation of "monitor*" as clinicaltrials.gov does not support term truncation. Instead, the search strategy includes variations of "monitor" in that the phrase "AND monitored AND monitoring" has been added to the 'other terms' line. This change has not produced any changes to the results returned by the search, leaving all other parts of the review unaffected by this change.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Blood Glucose; Blood Glucose Self-Monitoring; *Cystic Fibrosis [complications]; *Diabetes Mellitus; Retrospective Studies

### MeSH check words

Humans