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Continuous glucose monitoring systems for the diagnosis of cystic fibrosis-related diabetes (Protocol)

Ahmed MI, Fox R, Shinkins B, Sutton S, Tziaferi V, Gaillard EA

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TABLE OF CONTENTS

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[Diagnostic Test Accuracy Protocol]

Continuous glucose monitoring systems for the diagnosis of cystic fibrosis-related diabetes

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

Primary objective

- To assess the evidence on the accuracy of CGMS in detecting abnormalities of glycaemic control in children and adults with CF.

BACKGROUND

Cystic fibrosis (CF) is the most common autosomal recessive inherited condition in white populations; with a genetic carrier rate of 1 in 25 people, it affects around 1 in 2500 newborns in the UK (Farrell 2008; Ratjen 2003). It mainly affects the lungs, and the main cause of death is respiratory failure. This condition also affects the pancreas, particularly the β-cells, leading to cystic fibrosis-related diabetes (CFRD) due to insulin deficiency.

As the survival of people with CF has been improving over the last few decades, there has been a noticeable increase in the reported prevalence of CFRD. Almost half of adults with CF aged 20 years and older are estimated to have CFRD; the prevalence of CFRD and the mortality rate in adults with CFRD has been noted to increase with age (Lewis 2015). Increased awareness and screening for CFRD has also contributed to the increase in the reported prevalence of CFRD. Continuous glucose monitoring systems (CGMS) may help especially in the early diagnosis of glucose abnormalities in children with CF, potentially allowing earlier treatment of CFRD and better clinical outcomes.

Target condition being diagnosed

The onset of CFRD is insidious, and classical symptoms of diabetes may be absent. People with CF are more likely to present with CFRD when there is an increased insulin resistance such as during lung infections or while using steroids (Moran 2014). Microvascular complications including kidney disease and retinopathy, resulting from prolonged periods of hyperglycaemia may be

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less common in CFRD compared to the non-CF diabetic population (Landers 1997; Schwarzenberg 2007). However, CFRD is associated with an accelerated decline in lung function, a reduction in body mass index (BMI) (Lanng 1994; Moran 2010) and ultimately in worse survival. With longer survival in people with CF, there may be an increased prevalence of complications of CFRD, which can impact on survival and the quality of life (Koch 2001; Lewis 2015).

When people with CF are otherwise clinically stable, the diagnosis of CFRD is made as per standard American Diabetic Association (ADA) criteria (ADA 2016). Therefore, CFRD is diagnosed if on the oral glucose tolerance test (OGTT), the two-hour blood glucose is high (at least 11.1 mmol/L); there is a high fasting glucose of at least 7 mmol/L; HbA1C is increased at least 6.5%; or if there is a random blood glucose level of at least 11.1 mmol/L (random blood glucose is different to fasting blood glucose and is measured at any time of the day) with symptoms suggestive of hyperglycaemia or hyperglycaemic crisis. In people with CF who are acutely ill (individuals on intravenous antibiotics or glucocorticoids), the diagnosis of CFRD is made when the fasting plasma glucose levels are more than 7.0 mmol/ L or two-hour post-prandial plasma glucose levels more than 11.1 mmol/L persist for more than 48 hours (ADA 2016).

Index test(s)

Since 2000, CGMS have been available for managing diabetes mellitus (Gross 2000). They measure interstitial fluid glucose levels to provide semi-continuous information, which identifies fluctuations that cannot be identified with intermittent blood sugar monitoring (Langendam 2012).

Since the introduction of CGMS, there has been a significant improvement in the accuracy, user-friendliness and data analysis software along with a reduction in the size and cost of these devices (Damiano 2014; Pleus 2015). Most systems use a needle sensor, inserted under the skin, but non-invasive systems are also available. These systems measure the glucose concentration in the interstitial fluid that is triggered by applying a local electric current (iontophoresis) (Chase 2005). Currently, CGMS are available to individuals who use an electrochemical approach to glucose measurement. Many different approaches like micro-dialysis and fully implantable sensors have previously been tried with varying success rates (Garg 2004; Vaddiraju 2010; Valgimigli 2010).

Data from CGMS are presented by ambulatory glucose profile (AGP), this report includes a visual display of the glucose profile over the entire time duration of testing. As there are different CGMS currently used, there are variations in test methods. One parameter often used to characterise the analytical performance of CGMS is the mean absolute relative difference (MARD) between the CGMS readings (sometimes the median value is also used) and the values measured at the same time using a reference system (e.g. blood glucose levels). This parameter can be used to summarise results (Kropff 2015).

It is possible to use CGMS continuously or intermittently, but they are typically used over a period of three to seven days when clinical concerns regarding blood glucose control are raised, or to fine tune insulin treatment regimens. Although CGMS have been shown to have good repeatability and reliability (O'Riordan 2009), there is limited evidence on the accuracy of CGMS to diagnose CFRD. There are no agreed standard criteria for diagnosing CFRD using CGMS. As the ADA criteria are the clinical reference standard for CFRD (ADA 2016), the diagnostic criteria for a positive CGMS should be consistent with the above. The criteria for test-positivity for CFRD using CGMS in this review are a fasting glucose of greater than 7.0 mmol/L or a random glucose level greater than 11.1 mmol/L on more than one occasion.

Clinical pathway

People (both children and adults) with CF should be investigated for CFRD in any of the following situations (ADA 2016).

- Annual review for all children over 10 years of age
- Clinical concerns
- Finding of high blood glucose levels in any individual
- High glycated haemoglobin (HbA1c) greater than 6.5% (International Federation of Clinical Chemistry - IFCC HbA1c over 48 mmol/mol)
- Symptoms of hyperglycaemia
- Unexplained weight loss
- Unexplained reduction in lung function
- Prior to starting corticosteroids, overnight feeds, or before major surgery

The diagnosis of CFRD is made as per standard ADA criteria (ADA 2016) (see Target condition being diagnosed). Misdiagnosis of CFRD, both false positive and false negative, can occur. Missing a diagnosis or a delayed diagnosis can lead to worsening lung function and nutritional status, thereby having a negative impact on the clinical status and quality of life of people with CF.

Alternative test(s)

The ADA criteria recommend that CFRD should be diagnosed using the two-hour 75 g (1.75 g/kg) OGTT (ADA 2016). The OGTT also detects individuals with impaired glucose tolerance. It is important to note that, although the results of OGTT are not always reproducible and can vary over time (Ko 1998; Mueller-Brandes 2005; Sterescu 2010), it continues to be recommended in most consensus statements.

Using HbA1c to diagnose CFRD has been shown to be unreliable because it can be falsely low due to increased red blood cell turnover (Dobson 2004; Lanng 1995). A high HbA1c suggests hyperglycaemia, but a normal HbA1c does not exclude it.

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People with CF can have CFRD despite their fasting glucose levels or their random glucose levels being normal; the above tests have both low sensitivity and specificity for diagnosis of CFRD (Godbout 2008; Yung 1999).

Rationale

Due to improved survival of people with CF and increased screening for CFRD, the reported prevalence of CFRD is increasing (Lewis 2015). Earlier diagnosis of CFRD may help in the early initiation of treatment and better control of the blood sugars to improve clinical outcomes. Currently, CFRD is diagnosed as per the ADA criteria which include clinical symptoms in combination with OGTT, HBA1C and plasma glucose levels (ADA 2016).
In people with CF with both normal and altered glucose tolerance at OGTT, episodes of hyperglycaemia have been picked up on CGMS (Schiaffini 2010). The use of CGMS may therefore help to diagnose glucose abnormalities earlier in children with CF (Soliman 2014); however, there is limited evidence on its accuracy in people with CF.
The clinical utility of CGMS in predicting outcomes in CF is also unknown. Interstitial fluid blood glucose levels greater than 7.8 mmol/L on CGMS for more than 4.5% of the time have been noted to have an association with a decline in lung function and weight over the preceding year (Hameed 2010).

OBJECTIVES

Primary objective

- To assess the evidence on the accuracy of CGMS in detecting abnormalities of glycaemic control in children and adults with CF.

Secondary objectives

- To investigate the potential causes of heterogeneity [including age, severity of lung disease, glycaemic control, symptomatic and asymptomatic individuals, timing of testing (during stable disease or an infective exacerbation) and the type of CGMS] and their influence on the diagnostic accuracy of CGMS in CFRD.

- To identify gaps in the evidence and identify areas where further research is required.

METHODS

Criteria for considering studies for this review

Types of studies

We will include cross-sectional studies and prospective cohort studies that compare CGMS against the reference standard in the diagnosis of CFRD as outlined by the ADA criteria (ADA 2016). We will also include randomised comparisons of tests in which all participants have been cross-classified with a reference standard. We will exclude case-control studies, case reports, and studies where CGMS is performed retrospectively after an abnormal OGTT. We also plan to exclude systematic reviews, although we will extract any relevant primary studies.

Participants

We will include studies involving people (both children and adults) with CF in whom CFRD is suspected or who are being routinely screened for CFRD. The diagnosis of CF is confirmed by the presence of two disease-causing mutations, or by a combination of positive sweat test and associated clinical features of CF.

Index tests

The index test for this review is CGMS.

Target conditions

The target condition is CFRD.

Reference standards

The clinical reference standard is the diagnosis of CFRD as outlined by the ADA criteria (see Target condition being diagnosed).

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We will identify relevant studies from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Register using the term: cystic fibrosis-related diabetes [CFRD] and impaired glucose tolerance [IGT].
The Cystic Fibrosis Trials Register has been 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 has

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been identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group website.

We will also search the following databases, trials registries and resources:

- Cochrane Central Register of Controlled Trials (CENTRAL; all years) in the Cochrane Library www.cochranelibrary.com/;
- MEDLINE Healthcare Databases Advanced Search (HDAS) (hdas.nice.org.uk/ 1946 to present);
- Embase Healthcare Databases Advanced Search (HDAS) (hdas.nice.org.uk/ 1974 to present);
- ISRCTN registry (www.isrctn.org);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch).

See the appendices for the full search strategies (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We will review the reference lists of all included articles and relevant systematic reviews to identify any additional studies.

We will hand search two highly-relevant journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis* (last five years). We will also hand search the abstract books of the European Cystic Fibrosis Conference, the North American Cystic Fibrosis Conference and the major diabetology meetings (Diabetes UK, European Association for the Study of Diabetes, the ADA, and the International Society for Pediatric and Adolescent Diabetes) (last five years).

Data collection and analysis

Selection of studies

Two authors (MA, RF) will independently apply the selection criteria to determine the studies to be included in the review. We will perform the screening of title and abstracts and follow this by screening of full text articles. We will resolve differences in opinion through discussion, or if needed, by a third review author. We will use the kappa statistic to measure the inter-rater agreement for study selection (Cohen 1960), and detail reasons for any exclusions in a flow diagram.

Data extraction and management

We shall construct customised data extraction forms to facilitate independent data extraction. Two authors (MA, RF) will pilot this form using five initial studies and refine it, if and where necessary. In the case of any disagreements on the suitability of a study or its risk of bias, the authors plan to reach a consensus through discussion. In studies where the required information is missing, the review authors aim to contact the trial authors to seek this additional information.

We shall extract the following information for each study.

- Study information: first author, year of publication, country, language, objectives, inclusion and exclusion criteria and study design.
- Study participants: study population, included participants, age, incidence of acute pulmonary exacerbations, BMI, lung function, new isolation of bacterial pathogens.
- Information on the index test and reference standard: test methods, positivity threshold(s) used including how serial measurements were combined to inform the diagnosis, number of test failures and inconclusive results (and reasons for them), the number of measurements and the time-points at which measurements were taken and any adverse effects including infection, bleeding, irritation of skin, allergy to taping, pain and any issues on insertion. For each measurement recorded from the index test, we will note whether a comparative reference standard measurement was available.
- Number of true positives, true negatives, false positives and false negatives - we plan to use the above information to construct a 2 x 2 table for each measurement time-point. Where necessary and feasible, we will back-calculate this information from reported sensitivity, specificity and prevalence estimates.

Assessment of methodological quality

We will use the QUADAS-2 (quality assessment of diagnostic accuracy studies) tool to assess the risk of bias and concerns regarding applicability for all included studies. We will assess the risk of bias in each of the four key domains (participant selection, index test, reference standard, flow and timing) using the signalling questions (Whiting 2011); we will also assess any concerns regarding applicability in the first three domains.

We will produce graphs indicating the risk of bias in the Review Manager (RevMan) software and will present the overall scores for each domain (RevMan 2014). Two review authors (MA, RF) will independently assess all the included trials. We aim to resolve any potential disagreements by discussion or, where necessary, by a third review author.

We have detailed the components and signalling questions associated with each of the domains of the QUADAS-2 (Appendix 4).

Statistical analysis and data synthesis

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The diagnosis of CFRD is made as per standard ADA criteria (See Target condition being diagnosed). There are no agreed standard criteria for diagnosing CFRD on CGMS. As the ADA criteria is the clinical reference standard for CFRD (ADA 2016), the diagnostic criteria for a positive CGMS should be consistent with the above. The criteria for test-positivity for CFRD using CGMS in this review are a fasting glucose of greater than 7.0 mmol/L or a random glucose level greater than 11.1 mmol/L on more than one occasion.

We shall conduct the analyses in line with chapter 10 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010).

We shall use descriptive statistics to present a summary of the data extracted from each included study. The tables will report the participant sample size, study design and the methods or devices that are used to monitor continuous glucose levels. In addition, we will summarise the number of measurements and associated timings of measurements within each study. We shall extract binary diagnostic accuracy data from all included trials as 2 x 2 tables. Where we base the 2 x 2 tables on data from serial measurements, we will summarise the methods used to interpret serial measurements, e.g. the average of four serial measurements.

We expect that the positivity thresholds applied for the index test will vary across the included studies. In this case, we shall conduct the meta-analysis across all studies using the hierarchical summary receiver operating characteristic (HSROC) model (Rutter 2001) to estimate a summary curve using the NLMIXED procedure in SAS (SAS 2011). If different methods for interpreting serial measurements have been employed, we will only include studies using common methodology for meta-analysis. This may result in a number of subgroup meta-analyses. If there are a sufficient number of studies that report at common positivity thresholds, we will conduct subgroup meta-analyses using the bivariate method to provide pooled sensitivity and specificity estimates for each threshold (Reitsma 2005).

We will use RevMan to produce forest plots showing the variability of sensitivity and specificity across the included studies with corresponding 95% confidence intervals (CIs). We aim to break down the forest plots into subgroups where possible and necessary, e.g. for different positivity thresholds (Macaskill 2010).

Investigations of heterogeneity

We will initially assess for heterogeneity by visually examining the forest plots of sensitivities and specificities and the ROC (receiver operating characteristic) plots.

There are a number of possible factors that may account for between-study differences in the accuracy of CGMS. Where common differences in test methods (index test or reference standard) or study participants are evident, we will explore whether these factors result in notable differences in accuracy. In particular, we envisage that the following participant factors are likely to influence the accuracy of CGMS:

- age (all ages to be included);
- asymptomatic versus symptomatic individuals;
- severity of lung disease - mild lung disease (forced expiratory volume in one second (FEV_1) of 80% to 100% predicted) versus moderate disease (FEV_1 between 40% and 80% predicted) versus severe disease (FEV_1 less than 40% predicted);
- glycaemic control - HbA1c less than 7% versus HbA1c 7% to 8% versus HbA1c greater than 8%; and
- timing of CGMS - CGMS performed when participant is clinically stable versus during an episode of pulmonary exacerbation;
- type of CGMS.

Where the report breaks down the 2 x 2 data, or if a subset of the included studies is limited to a particular subgroup (e.g. adolescents), we will carry out subgroup meta-analyses to explore whether there are notable differences in the pooled estimates of sensitivity and specificity. If sufficient information for a particular factor is available across all studies, we will perform meta-regression which involves adding the potential source(s) of heterogeneity as a covariate to the meta-analysis model.We will use the Metadas Macro in SAS to perform this analysis.

Sensitivity analyses

If necessary and appropriate, we shall perform sensitivity analyses excluding studies that are at a high risk of bias for at least one domain of the QUADAS-2 tool (see Assessment of methodological quality).

Assessment of reporting bias

There is no consensus on the ideal methodology to identify reporting bias in reviews of diagnostic test accuracy. We shall not be using existing analytical tools such as funnel plots as there is lack of evidence of their usefulness in these reviews (Deeks 2005). We shall perform a comprehensive search for all eligible studies (Search methods for identification of studies).

Summary of findings tables

We will prepare a summary of findings table, this shall include the review question, any limitations noted while assessing the risk of bias and applicability, or excessive heterogeneity and the estimates of the accuracy of CGMS.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. Search strategies for MEDLINE and Embase

MEDLINE and Embase searches will be run on the NICE Evidence Healthcare Databases Advanced Search (HDAS) Platform. Some of the search lines have been specially adapted for this database - where MEDLINE defaults to five characters after the star in truncation unless a larger number is specified. So in terms where a larger number of characters was considered to be possible we used *9. HDAS will not search two truncated terms in inverted commas for phrase searching, so we have used adj as an alternative.

MEDLINE Search	
#	**Search term**
1	exp "CYSTIC FIBROSIS"/
2	(cystic* ADJ5 fibro*).af
3	(Mucoviscido*).af
4	(fibrocyst* ADJ5 pancrea*9).af
5	(1 OR 2 OR 3 OR 4)
6	exp "DIABETES MELLITUS"/
7	(diabet*).af
8	(glucose).af
9	(hyperglyc*9).af
10	(hypoglyc*9).af
11	(igt).af
12	(ogtt).af
13	(insulin*).af
14	(postprandial*).af
15	("post prandial*").af
16	exp "GLUCOSE TOLERANCE TEST"/
17	exp "GLUCOSE INTOLERANCE"/
18	exp HYPERGLYCEMIA/

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(*Continued*)

19	exp GLUCOSE/
20	exp BLOOD GLUCOSE/
21	exp HYPOGLYCEMIA/
22	exp INSULIN/
23	("after food").af
24	("after eating").af
25	exp POSTPRANDIAL PERIOD/
26	(7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 2O OR 21 OR 22 OR 23 OR 24 OR 25)
27	(5 AND 26)
28	(cfrd*).af
29	(26 OR 28)
30	exp "BLOOD GLUCOSE SELF-MONITORING"/
31	(glucose ADJ5 monitor*).af
32	(sugar* ADJ5 monitor*).af
33	(hba* ADJ5 monitor*).af
34	(hba* ADJ5 sensor*).af
35	(glucose ADJ5 sensor*).af
36	(sugar* ADJ5 sensor*).af
37	(cgm OR cgms).af
38	(continuous*9 ADJ5 monitor*).af
39	(glucowatch*).af
40	(navigator*).af
41	(medtronic).af

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(*Continued*)

42	(glucosemeter*).af
43	(guardian*).af
44	(dexcom).af
45	(minimed*).af
46	(enlite).af
47	(animas).af
48	(vibe).af
49	(30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 40 OR 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48)
50	(49 AND 29)

Embase Search	
#	**Search term**
1	exp "CYSTIC FIBROSIS"/
2	(cystic* ADJ10 fibro*).af
3	(Mucoviscido*).af
4	(fibrocyst* ADJ10 pancrea*9).af
5	(1 OR 2 OR 3 OR 4)
6	exp "DIABETES MELLITUS"/
7	exp "ORAL GLUCOSE TOLERANCE TEST"/
8	exp "GLUCOSE BLOOD LEVEL"/
9	exp "ORAL GLUCOSE TOLERANCE TEST"/
10	exp GLUCOSE/
11	exp INSULIN/

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(*Continued*)

12	exp “IMPAIRED GLUCOSE TOLERANCE”/
13	exp HYPERGLYCEMIA/
14	exp HYPOGLYCEMIA/
15	exp “POSTPRANDIAL STATE”/
16	(diabet*).af
17	(glucose).af
18	(hyperglyc*9).af
19	(hypoglyc*9).af
20	(igt).af
21	(ogtt).af
22	(insulin*).af
23	(postprandial*).af
24	(“post prandial*”).af
25	(“after food”).af
26	(“after eating”).af
27	(6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26)
28	(cfrd*).af
29	(5 AND 27)
30	exp “BLOOD GLUCOSE SELF-MONITORING”/
31	(glucose ADJ5 monitor*).af
32	(sugar* ADJ5 monitor*).af
33	(hba* ADJ5 monitor*).af
34	(hba* ADJ5 sensor*).af

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(*Continued*)

35	(glucose ADJ5 sensor*).af
36	(sugar* ADJ5 sensor*).af
37	(cgm OR cgms).af
38	(continuous*9 ADJ5 monitor*).af
39	(glucowatch*).af
40	(navigator*).af
41	(medtronic).af
42	(glucosemeter*).af
43	(guardian*).af
44	(dexcom).af
45	(minimed*).af
46	(enlite).af
47	(animas).af
48	(vibe).af
49	(30 OR 31 OR 32 OR 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 OR 46 OR 47 OR 48)
50	(28 AND 29)
51	(49 AND 50)

Appendix 2. Search strategy for CENTRAL

CENTRAL search	
#	**Search term**
1	MeSH descriptor: [Cystic Fibrosis] explode all trees
2	cystic* near/5 fibro*

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(*Continued*)

3	mucoviscido*
4	fibrocyst* near/5 pancrea*
5	#1 or #2 or #3 or #4
6	MeSH descriptor: [Diabetes Mellitus] explode all trees
7	MeSH descriptor: [Glucose Tolerance Test] explode all trees
8	MeSH descriptor: [Glucose Intolerance] explode all trees
9	MeSH descriptor: [Hyperglycemia] explode all trees
10	MeSH descriptor: [Blood Glucose] explode all trees
11	MeSH descriptor: [Glucose] explode all trees
12	MeSH descriptor: [Hypoglycemia] explode all trees
13	MeSH descriptor: [Insulin] explode all trees
14	MeSH descriptor: [Postprandial Period] explode all trees
15	diabet* or glucose* or hyperglyc* or hypoglyc* or igt or ogtt or insulin* or postprandial*
16	"post prandial*"
17	"after food"
18	"after eating"
19	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20	#5 and #19
21	cfrd
22	#20 or #21
23	MeSH descriptor: [Blood Glucose Self-Monitoring] explode all trees
24	glucose near/5 monitor*
25	sugar* near/5 monitor*
26	hba* near/5 sensor*

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(*Continued*)

27	glucose near/5 sensor*
28	sugar* near/5 sensor*
29	cgm or cgms
30	continuous* near/5 monitor*
31	glucowatch* or navigator* or medtronic or glucosemeter* or guardian* or dexcom
32	minimed* or enlit or animas or vibe
33	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
24	#22 and #33

Appendix 3. Search methods - electronic searching

Database/ Resource	Strategy
ISRCTN registry	(”cystic fibrosis“) AND (glucose OR diabet* OR insulin OR sugar* OR hba1C OR glucowatch OR postprandial* OR cgm OR cgms OR navigator* OR hyperglyc* OR hypogly* OR igt OR ogtt OR ”post prandial*“ OR ”after food“ OR ”after eating“ OR Medtronic OR glucosemeter OR guardian* OR dexcom OR minimed* OR enlite OR animas OR vibe) OR (”mucoviscido*) AND (glucose OR diabet* OR insulin OR sugar* OR hba1C OR glucowatch OR postprandial* OR cgm OR cgms OR navigator* OR hyperglyc* OR hypogly* OR igt OR ogtt OR “post prandial*” OR “after food” OR “after eating” OR Medtronic OR glucosemeter OR guardian* OR dexcom OR minimed* OR enlite OR animas OR vibe) OR (“fibrocyst* pancrea*”) AND (glucose OR diabet* OR insulin OR sugar* OR hba1C OR glucowatch OR postprandial* OR cgm OR cgms OR navigator* OR hyperglyc* OR hypogly* OR igt OR ogtt OR “post prandial*” OR “after food” OR “after eating” OR Medtronic OR glucosemeter OR guardian* OR dexcom OR minimed* OR enlite OR animas OR vibe)
ClinicalTrials.gov	(“cystic fibrosis” OR mucoviscido* OR “fibrocyst* pancrea*”) AND (glucose OR diabet* OR insulin OR sugar* OR hba1C OR glucowatch OR postprandial* OR cgm OR cgms OR navigator* OR hyperglyc* OR hypogly* OR igt OR ogtt OR “post prandial*” OR “after food” OR “after eating” OR Medtronic OR glucosemeter OR guardian* OR dexcom OR minimed* OR enlite OR animas OR vibe)

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(*Continued*)

WHO International Clinical Trials Registry Platform (ICTRP)	("cystic fibrosis" OR mucoviscido* OR "fibrocyst* pancrea*") AND (glucose OR diabet* OR insulin OR sugar* OR hba1C OR glucowatch OR postprandial* OR cgm OR cgms OR navigator* OR hyperglyc* OR hypogly* OR igt OR ogtt OR "post prandial*" OR "after food" OR "after eating" OR Medtronic OR glucosemeter OR guardian* OR dexcom OR minimed* OR enlite OR animas OR vibe)

Appendix 4. Assessment of methodological quality : Quadas 2 Criteria

Domain	1: Participant selection	2: Index Test	3: Reference Standard	4: Flow and timing
Signalling questions and criteria	*Signalling question 1: Was a consecutive or random sample of participants enrolled?* • Yes: if the study clearly stated that enrolment was consecutive or random. • No: if the above condition was not met. • Unclear: insufficient information available to answer yes or no.	*Signalling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?* • Yes: if the study states that CGMS was performed prior to assessment of ADA criteria or that the interpretation of the CGMS was blinded to the results of the reference standard. • No: if the CGMS results were interpreted with the knowledge of the results of the reference standard. • Unclear: insufficient information available to answer "yes" or "no".	*Signalling question 1: Is the reference standard likely to correctly classify the target condition?* • Yes: if the reference standard used was consistent with the ADA criteria in the diagnosis of CFRD. • No: if the above condition is not met. • Unclear: insufficient information available to answer "yes" or "no"	*Signalling question 1: Was there an appropriate interval between index test (s) and reference standard?* • Yes: if the CGMS was performed within three months of the reference test. • No: if the reference test for all participants was performed more than three months after the CGMS. • Unclear: if not reported or cannot be determined
	Signalling question 2: Did the study describe clear inclusion criteria for participants with suspected CFRD? • Yes: specific inclusion criteria were described in the study methodology.	*Signalling question 2: If a threshold was used, was it pre-specified?* • Yes: thresholds were used and clearly defined and pre-specified. • No: if the above conditions were not	*Signalling questions 2: Were the reference standard results interpreted without knowledge of the results of the index test?* • Yes: if the reference standard results were interpreted without the knowledge of CGMS	*Signalling question 2: Did all participants receive a reference standard?* • Yes: if all participants had investigations to diagnose CFRD according to the ADA criteria.

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(*Continued*)

	• No: no inclusion criteria described. • Unclear: insufficient information available	met. • Unclear: insufficient information available to answer "yes" or "no".	results. • No: if the above condition is not met. • Unclear: insufficient information available to answer "yes" or "no"	• No: if the above condition is not met. • Unclear: insufficient information available to answer "yes" or "no".
	Signalling question 3: Did the study avoid inappropriate exclusions? • Yes: if all people in whom CFRD was suspected or screened were included. • No: if the above condition was not met. • Unclear: if there was no description of the inclusion and exclusion criteria.			*Signalling question 3: Did all participants receive the same reference standard?* • Yes: if all participants had investigations to diagnose CFRD according to the ADA criteria. • No: if the above condition is not met. • Unclear: insufficient information available to answer "yes" or "no".
	Signalling question regarding case-control design has been excluded, as these studies will be excluded from the review.			*Signalling question 4: Were all participants included in the analysis?* • Yes: if all participants were included in the final statistical analysis. • No: if the above condition is not met. • Unclear: insufficient information available to answer "yes" or "no".
Risk of bias	*Could the selection of participants have introduced bias?* • High risk of bias: at least one question was scored as 'No' • Low risk of bias: all questions were scored 'Yes', or a maximum of one question unclear • Unclear risk of	*Could the conduct or interpretation of the index test have introduced bias?* • High risk of bias: either of signalling questions 1 or 2 answered "no". • Low risk of bias: signalling questions 1 and 2 are both answered "yes".	*Could the reference standard, its conduct, or its interpretation have introduced bias?* • Low risk: signalling questions 1 and 2 are both answered "yes". • High risk: either of signalling questions 1 or 2 answered "no" • Unclear risk of	*Could the participant flow have introduced bias?* • High risk of bias: at least one question was scored as 'No'. • Low risk of bias: all questions were scored 'Yes', or a maximum of one question with unclear.

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(*Continued*)

	bias: insufficient information available to make a judgement	• Unclear risk of bias: insufficient information available.	bias: insufficient information available.	• Unclear risk of bias: insufficient information available to make a judgement.
Applicability	*Are there concerns that the included participants and setting do not match the review question?* • Low concern: if the study population meets the defined criteria • High concern: participants as described above are not included • Unclear: insufficient information available to make a judgement.	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?* • Low concern: if CGMS was performed and interpreted correctly as per the review question. • High concern: if the above condition was not met. • Unclear: insufficient information available.	*Are there concerns that the target condition as defined by the reference standard does not match the question?* • Low concern: if the reference standard was the ADA criteria and if the target condition was suspected CFRD in an individual as defined in our protocol. • High concern: if the above conditions are not met. • Unclear: insufficient information available.	

WHAT'S NEW

Last assessed as up-to-date: 1 February 2018.

Date	Event	Description
15 March 2018	Amended	Reference corrected.

CONTRIBUTIONS OF AUTHORS

TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage	
draft the protocol	Molla Imaduddin Ahmed, Rachel Fox, Bethany Shinkins,Sarah Sutton
Review stage	

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run searches	Sarah Sutton
select which trials to include (2 + 1 arbiter)	Molla Imaduddin Ahmed, Rachel Fox, Erol Gaillard
extract data from trials (2 people)	Molla Imaduddin Ahmed, Rachel Fox
enter data into RevMan	Molla Imaduddin Ahmed, Rachel Fox
carry out the analysis	Molla Imaduddin Ahmed, Rachel Fox, Bethany Shinkins
interpret the analysis	Molla Imaduddin Ahmed, Rachel Fox
draft the final review	Molla Imaduddin Ahmed, Rachel Fox, Vaya Tziaferi, Erol Gaillard
update the review	Molla Imaduddin Ahmed, Rachel Fox

DECLARATIONS OF INTEREST

Molla Ahmed: none known.

Rachel Fox: none known.

Bethany Shinkins: none known.

Sarah Sutton: received travel expenses as a Librarian Advisor for UpToDate from 2014 to 2016.

Vaya Tziaferi: none known.

Erol Gaillard: I undertook consultancy work for Boehringer Ingelheim in November 2016 and Anaxsys in July 2018 with money paid to the institution (University of Leicester). I am named in investigator-led research grants from Circassia and Gilead and research collaboration with Medimmune; all monies from these were received by my institution (University of Leicester). I have received travel grants from Vertex to attend international CF conferences.

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