Protocol for:

A review to examine the research question: What are the outcomes related to efficacy reported in trials of interventions for cystic fibrosis in pre-school children aged 0-5?

Jared Murphy, Alan R Smyth, Ian P Sinha, Nikki Jahnke, Tracey Remmington, Kevin W Southern.

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

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

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

Eligibility criteria:

Studies to be reviewed: Cochrane systematic reviews of interventions and the randomised controlled trials which they include in their analysis. Possible ad hoc decision depending on number of trials found to be eligible: only include those RCTs with a low risk of bias. It has not yet been fully decided what the cut off number will be, however the process of this decision making will be documented for transparency.

Children aged 0-5 with confirmed diagnosis of cystic fibrosis who have participated in randomised controlled trials of interventions.

Exclusion criteria:

Papers which do not include 0-5 year olds as recruited participants, regardless of whether they were eligible to join. If none were recruited, the paper will be excluded.

Outcomes being looked for: outcomes relating to efficacy of interventions.

1. Frequency of what efficacy outcomes are measured by the systematic reviews, and their included trials.
2. Are all outcomes which are stated in the systematic review or RCT's protocol (where available) then reported in papers?

3. Quality of trials in this age group- risk of bias analysis for the included RCTs (not systematic reviews)
4. Do the systematic reviews and trials examine just 0-5 year olds, or also older children or adults as well?

Search methods

We will identify all Cochrane systematic reviews which meet the above criteria of examining an intervention in 0-6 year olds with CF. This will be done through a search of the Cochrane library of systematic reviews.

The Cochrane database of systematic reviews will be searched with the term 'cystic fibrosis'.

There will be no limitation on publication date or language. Cross-over studies will also be considered.

Once the search term is applied, titles, abstracts and 'characteristics of studies' section will be screened for eligibility. Following that, full papers will be screened to include/exclude them from analysis.

To identify the RCTs included in these systematic reviews, the reviews will be read and their bibliographies screened to identify included trials. These will then be obtained. The titles, abstracts and full texts of the individual trials will be also be screened according to eligibility criteria. This is to avoid the assumption that they will automatically be eligible by virtue of being in an eligible systematic review, which could result in bias in our searching. The protocols for each paper will also be obtained where possible in order to answer outcome 2. The RCTs will be found before the data is extracted from the included systematic reviews (see below) in order to keep the identification of eligible sources of info as a single process and not repeating some processes. The same reasoning applies to the data extraction.

How are we going to measure the above outcomes?

1. Frequency of what outcomes are measured by the systematic reviews, and their included trials.
   Initially recorded as a list, which can then be tallied then be presented numerically in a table.

2. Are all outcomes which are measured then reported in papers?

Paper	Are all outcomes reported in results?	If no- which outcomes are not reported in results
W et al.	No	Lung clearance index
X et al.	Yes	

   Table A.
   A further tally may be made of the outcomes which are not reported (third column), with the possibility of identifying any outcomes which may be missed more frequently.

3. Quality of trials in this age group- do the included RCTs already have a risk of bias evaluation as part of their Cochrane review. If for whatever reason they don't have risk of bias evaluation, or it is not available, we will repeat the risk of bias evaluation ourselves using the Cochrane risk of bias tool.

4. Do the systematic reviews and trials examine just 0-5 year olds, or also include 6-12 year olds, 12-18 year olds or adults as well?

   For each included systematic review and RCT, create a row in a table and mark a tally when each age group is included. These tallies can then be presented as numbers For example:

Paper	0-5 year olds	6-12 year olds	12-18 year olds	Over 18 years old
Y et al.	/	/	/	/
Z et al.	/	/		

Table B.

Data extraction

Round 1- Systematic reviews

Firstly, the frequency of outcomes reported by the included systematic reviews will be recorded according to the number of systematic reviews which report them in their results section. For example, if 2 systematic reviews report on the outcome: FEV1, the frequency of FEV1 will be 2. This can be presented in a table such as this example:

Outcome	Number of times reported in a review's results section
FEV1% of predicted	6
Weight (kg)	4

Table C.

Each systematic review will also be checked to see if each outcome which it says it intends to measure in its methods section is indeed reported in its results section. This is an assessment of reporting bias. It can be gathered in a table such as Table A above.

Round 2- RCTs

Once data has been extracted from the included systematic reviews, each of the RCTs which they include will be identified, obtained and screened for eligibility.

- A) Quality of studies

This is an additional outcome which will be measured for RCTs, but not systematic reviews.

Once RCTs are obtained, each will be appraised using GRADE approach. This is to test the quality of the evidence provided by the trials. Depending on the number of trials identified, this can be used to identify high quality trials, which will then be the ones selected for data extraction, if there is a sufficient number of high quality trials (mentioned above).

If the overall number of trials is below the cut-off which is to be decided, all trials will be included in subsequent data extraction. Frequency of each outcome can then be recorded with respect to the quality of the trials which report them. Please see example table below.

Number of trials including this outcome			
Risk of bias	Very Low	Low	Moderate
Outcome			
FEV1% predicted	4	5	2
Number of exacerbations	2	6	4

Table D

- B) Data extraction

Once the risk of bias appraisal is finished and included trials are selected, the same outcomes will be extracted as were from the systematic reviews in round 1, but this time for each RCT.

The frequency of each outcome will be recorded as we go through each RCT. See table C for similar example.

The outcomes which are said to be measured in the methods will be checked to see if they are all reported in the results sections of the RCTs. See table D for similar example. This is an assessment of reporting bias.

Each outcome recorded will also be categorised into the relevant type/domain of outcome, as described by the COMET initiative (1).

Statistical analysis

This form of data extraction is largely identifying which outcomes are reported and counting the frequency/number of included trials which report each outcome. There is not an intervention or control group and therefore no comparison made. This means statistical analysis may not provide much value to the interpretation of data.

Dealing with difficulties

In order to minimise mistakes or biases, the data extraction and quality appraisal will be performed independently by two of the authors. If there is any disagreement between authors, discussion will aim to reach a consensus, with a third author independently arbitrating.

1. COMET. Outcome Classification comet-initiative.org: COMET Initiative; 2018 [Available from: http://www.comet-initiative.org/OutcomeClassification.