

**TITLE: A SYSTEMATIC REVIEW TO IDENTIFY HOW THE CURRENT CLINICAL TRIALS LANDSCAPE REFLECTS THE JAMES LIND ALLIANCE TOP 10 RESEARCH PRIORITIES FOR CYSTIC FIBROSIS.**

**PROTOCOL**

**AUTHORS:** IS Kalaitzis, NJ Rowbotham, S Smith\*, AR Smyth

\*Corresponding author

Sherie Smith

**ADDRESS:** Evidence Based Child Health Group, Division of Child Health, Obstetrics & Gynaecology, E Floor East Block, Queens Medical Centre, Nottingham NG7 2UH.

Email: sherie.smith@nottingham.ac.uk

**AFFILIATION:** Evidence Based Child Health Group, University of Nottingham, UK

**Abbreviations:**

JLA: James Lind Alliance

PSP: Priority Setting Partnership

MDT: Multi-disciplinary Team

**BACKGROUND**

CF is a life limiting, autosomal recessive condition. It affects 1 in 2000-3000 newborns in the European Union and 1 in 3500 newborns within the United States of America<sup>1</sup>. Currently, within the UK around 10,000 people suffer from CF<sup>2</sup>.

CF is a multisystem disorder which requires long term, specialist multidisciplinary team (MDT) care in order to manage the many treatment decisions and aspects of CF disease effectively. Treatment varies from patient to patient according to the nature and severity of their symptoms and includes but is not limited to airway clearance, pancreatic enzyme replacement, dietary supplementation, antibiotics and nebulisers.

There are many uncertainties regarding Cystic Fibrosis (CF) treatment. Well-designed clinical trials should focus on questions which are important to patients and clinicians. Recently, the first James Lind Alliance (JLA) Priority Setting Partnership (PSP) in CF was completed<sup>3</sup>, bringing clinicians, patients and carers together to identify the Top 10 research priorities. Now that we know which treatment uncertainties are most important to the CF community, we want to examine how these priorities are reflected in the current clinical trial landscape. We aim to do this by carrying out a systematic review of the clinical trials registries and mapping the results to the James Lind Top ten.

## **REVIEW QUESTION**

The review aims to identify current clinical trials on cystic fibrosis treatments and to find out how well these trials reflect the James Lind Alliance top ten priorities for research.

## **SEARCHES**

Databases: PubMed; Australia and New Zealand Clinical Trials Register; EU Clinical Trials register; Clinicaltrials.gov; ISRCTN

Dates searched: 1<sup>st</sup> January 2016 – 9<sup>th</sup> November 2017

Language restrictions: only those trials published in English

The terms “cystic fibrosis” and where possible “interventional” were used.

Non registry studies were found by contacting relevant members of the Cystic Fibrosis Foundation regarding the Success with Therapies Research Consortium (STRC), CF health hub.

Search strategies are in Appendix 1

## **CONDITION BEING STUDIED**

Treatment interventions for adults and children with cystic fibrosis.

## **PARTICIPANTS/POPULATION**

Participants diagnosed with CF (through genetic testing or sweat testing) and of any age. Studies including other conditions but where CF patients are analysed as a specific subgroup were included if they met the rest of the inclusion criteria.

## **INTERVENTION(S)**

Studies of treatment interventions in CF will be included. Studies involving trials of combinations of interventions, timings and duration of intervention and stopping interventions will also be included.

Studies covering diagnosis, newborn screening or those concerning diagnostic test accuracy will be excluded as well as those concerning policy, evaluation of the training of physicians or organisation of care.

The interventions we include will likely fall into these categories: drugs interventions (antibiotics and CFTR modulators), behavioural interventions (supportive care etc), dietary interventions (vitamin D, fibre etc), device or web based interventions (trackers, smartphone apps or virtual reality etc) and other interventions such as home monitoring and exercise for example.

## **COMPARATOR(S)/CONTROL**

The comparator will be either be a placebo, usual treatment or no treatment.

## **TYPES OF STUDY TO BE INCLUDED**

The study type we are looking for is interventional clinical trials of treatments for CF. We will include completed and ongoing trials.

## **CONTEXT**

Setting includes inpatient and outpatient treatments in primary and secondary care and includes any trial that confers patient benefit.

## **PRIMARY OUTCOME(S)**

The primary outcome is any clinically meaningful outcome which reflects patient benefit. We expect the outcomes to fall into the following categories but this list is not exclusive:

- Lung Function (e.g. FEV1, FVC, Lung clearance index etc)
- Health-related quality of life validated measures (e.g. Cystic Fibrosis Questionnaire (CFQ) 26)
- Respiratory symptom outcomes (e.g. Respiratory and Systemic Symptoms Questionnaire RSSQ)
- Hospitalisation (e.g. number of nights inpatient)
- School/Work attendance (e.g. number of days missed)

- Nutrition & Growth (e.g. weight gain, height, fat)
- Radiological (e.g. bone mineral density)
- Sputum properties
- Pulmonary exacerbations (measured by frequency of exacerbation or time to next exacerbation etc)
- Antibiotic use (e.g. number of courses, combinations, delivery method)
- Adverse effects (toxicity & allergy, microbiology, complication of delivery)
- Exercise tolerance
- Sweat chloride as a measure of CFTR function
- Mucus clearance
- Nasal symptom scores
- Bowel symptoms (e.g. stool frequency, abdominal pain etc)
- Treatment burden
- Treatment adherence
- Cost

## **SECONDARY OUTCOME(S)**

There are no secondary outcomes

## **DATA EXTRACTION**

Electronic search results will be collated into an Excel document. Studies found through other searches will be assembled into a separate Excel document.

Where possible, data on study title, recruitment, intervention, outcome measures, sponsor/collaborators/funding and study type will be recorded in the Excel Document.

For all studies, duplicates will be checked for manually and excluded.

The title/abstract of each study will be scanned by one reviewer and trials that are not interventional will be excluded. A second reviewer will check those records where there is uncertainty.

Studies which are deemed to fulfil the inclusion criteria from the title and abstract will be retrieved in full and scanned again for inclusion. Trials excluded at this stage will be listed with the reason for exclusion.

Data will be collected on the trial characteristics, the sponsor of the trial and the funding source.

## **STRATEGY FOR DATA SYNTHESIS**

The primary aim of the review is to match the identified clinical trials with the top ten priorities for research in CF which were the result of a James Lind Alliance Priority Setting Partnership.

All available information on the trials will be reviewed in order to extract the main aims of the trial and to make a decision on the most accurate match of each study to the Top 10 research priorities. Matching will be recorded in Excel.

A second reviewer will check the matching decisions (NR) to ensure matching results are as accurate as possible. Any trials with matches made to the Top 10 priorities deemed by the first reviewer to be uncertain and needing a second opinion will be flagged. A final decision will be made by discussion.

## **ANALYSIS OF SUBGROUPS OR SUBSETS**

Matching of trials to the James Lind Alliance top ten will be done for each priority in turn.

## **DISSEMINATION PLANS**

We intend to publish the results in a peer reviewed journal and present at the European CF Society meeting.

## **KEYWORDS**

Cystic fibrosis

Systematic review

Priority setting

Clinical trial

Thematic analysis

## REFERENCES

1. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax* 2016;**71**(5):454-61.
2. Rowbotham NJ, Smyth AR. The patient voice in research - Supporting actor or starring role? *Journal of cystic fibrosis* 2017;**16**(3):313-14.
3. Rowbotham NJ, Smith S, Leighton PA, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax* 2017.

## **APPENDIX 1**

Search strategies used in the systematic review

### ClinicalTrials.gov

Condition or disease: 'cystic fibrosis', Study Type: 'Interventional Studies', First posted: '01/01/2016' to '09/11/2017'

### ISRCTN

Condition: 'cystic fibrosis', Date applied '01/01/2016' to '09/11/2017' and Overall trial start date '01/01/2016' to '09/11/2017'

### EU CLINICAL TRIALS REGISTER

Search term 'cystic fibrosis', Date range '2016/01/01' to '2017/11/09'

### Pubmed

'cystic fibrosis' in title/abstract, Date- Publication '2016/01/01' to '2017/11/09'

Article types: 'Clinical trials'

(cystic fibrosis[Title/Abstract]) AND ("2016/01/01"[Date - Publication] : "2017/11/09"[Date - Publication])

### ANZCTR

Search term 'cystic fibrosis', Study type: 'Interventional', Trial start date '01/01/2016' to '09/11/2017' and registration date '01/01/2016' to '09/11/2017'