Clinimetric Analysis of Outcome Measures for Airway Clearance in Adults with Cystic Fibrosis: A Systematic Review

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Research

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Abstract

Background

Airway clearance techniques (ACTs) are integral to cystic fibrosis (CF) management. However, there is no consensus as to which outcome measures (OMs) are best for assessing ACT efficacy.

Objectives: To summarise OMs that have been assessed for their clinimetric properties (including validity, feasibility, reliability & reproducibility) within the context of ACT research.

Methods

Eligibility Criteria - Any parallel or cross-over randomised controlled trial (RCT) investigating outcome measures for ACT in the CF population.

Information sources: Five medical databases; clinicaltrials.gov; abstracts from international CF conferences.

Risk of Bias - The authors planned to independently assess study quality and risk of bias using the COSMIN risk of bias checklist with external validity assessment based upon study details (participants and study intervention).

Synthesis of Results – Two review authors (GS and MJ) independently screened search results against inclusion criteria, further data extraction was planned but not required.

Results

Included studies - No completed RCTs from the 187 studies identified met inclusion criteria for the primary or post-hoc secondary objective. Two ongoing trials were identified.

Discussion

Limitations of evidence: The search strategy may have missed some lesser-known terms for ACT or manuscripts reporting clinimetric properties solely within text. Studies validating outcome measures for use in other aspects of CF, which may be relevant to ACT, are not included.

Interpretation - High-quality RCTs are urgently needed to investigate & validate the clinimetric properties of OMs used to assess ACT efficacy. With the changing demographics of CF combined with the introduction of CFTR modulator therapies, an accurate assessment of the current benefit of ACT or the effect of ACT withdrawal is a high priority for clinical practice and future research and OMs which have been validated for this purpose are essential.

Other

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Introduction

RATIONALE

Cystic fibrosis (CF) is a genetic disorder of ion transport across cell membranes affecting over 10,650 people in the UK[1]. The CF genetic defect causes organ damage leading to significant morbidity and premature mortality with the most common cause of death being respiratory complications[1, 2]. Within the CF lung, airways are dehydrated and viscous secretions which are difficult to clear create airway obstruction, mucus plugging and an ideal environment for infections[2]. Removal of these secretions using a combination of airway clearance techniques (ACTs) or chest physiotherapy and mucoactive agents is key to preventing recurrent infections and airway inflammation which can cause lung damage leading to respiratory failure and death[2].

There are several ACT techniques (also known as chest physiotherapy) in use, ranging from simple breathing techniques such as the Active Cycle of Breathing Techniques (ACBT) or Autogenic Drainage (AD), hand-held devices such as the Acapella™ or Aerobika™ to high-tech machines such as the high frequency chest wall oscillator (HFCWO) which have been designed to aid clearance. Currently no one technique is advocated over another for people with CF[3] as data are lacking to guide this; one research study over the course of a year comparing five ACT modalities (ACBT, AD, positive expiratory pressure (PEP) and two oscillatory PEP devices) demonstrated that no one technique was superior to others[4].

Historically, the spirometric measure, forced expiratory volume in one second (FEV_1) has been utilised most commonly by the CF community as a clinical and research outcome[5]. CF ACT-specific research has followed this practice, using FEV_1 alongside expectorated sputum wet weight as outcome measures, although data specifically evaluating these outcomes for ACT assessment is lacking. Additionally, some possible flaws in their use for this context have been reported[3, 4, 6, 7]. These include FEV_1 being effort-dependent[8], and possibly not sensitive enough to pick up changes in subjects with well-preserved lung function[5, 7]; and sputum weight being subject to the will/ability of the person to expectorate and not swallow secretions[6].

Due to the potential flaws in these traditional outcome measures, debate exists within the CF community as to what is the best outcome measure to use for ACT research[6, 7]. In fact, several Cochrane reviews regard this as an unmet need, suggesting that further work is necessary to identify the most appropriate OMs for the assessment of ACT efficacy[6, 9]. There has been recent growing interest in outcome measures for both observational and interventional studies in CF including the lung clearance index (LCI) derived from a multiple breath washout (MBW) test, hyperpolarised gases, magnetic resonance imaging (MRI) amongst others. However, whether these are appropriate to assess the effect of ACTs may not have been fully confirmed.

Clinimetric evaluation involves investigating whether an outcome measure has been validated for use with a specific construct e.g. to assess airway clearance effect in people with CF[10]. This entails investigating different measurement properties for the outcome. The COnsensus-based Standards for the selection of health status Measurement InstrumeNts (COSMIN) study used a Delphi approach to reach a consensus on taxonomy, definitions and terminology of measurement properties[11], thus offering a standardised definition for use. In broad terms the main measurement properties can be classified as reliability or reproducibility ("the degree to which the measure is free from measurement error"[11]); responsiveness ("the ability of an instrument to detect change over time in the construct to be measured"[11]) and validity ("the degree to which an instrument truly measures the construct(s) it purports to measure"[11])[10].

With this systematic review we sought to collate clinimetric evidence for the outcome measures used in CF ACT. Such a review is warranted to enable clinicians and researchers to assess the appropriateness of measures they may select to analyse the effects of ACT for people with CF and to identify areas requiring further work.

OBJECTIVES OF THE REVIEW

The primary objective of the review was to investigate the clinimetric properties of the outcome measures of FEV_1 and sputum weight, in order to answer the research question "how reliably does a change in FEV_1 or sputum weight indicate effective airway clearance in people with cystic fibrosis?".

A secondary objective was added *post hoc* when no eligible studies were identified to answer our primary objective, as suggested in the Cochrane guidance on reporting empty reviews[12]. This secondary objective was to increase our literature search to identify *any* outcome measures which had been assessed for their clinimetric properties in the context of airway clearance assessment.

Methods

The protocol for this review was developed following the guidance set out in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist[13], the COSMIN guideline for systematic reviews of patient-reported outcome measures (PROMs)[14] and advice on assessing the quality of studies assessing measurement instruments[15]. The 10-step process for completing a systematic review described by COSMIN[14] (Fig. 1) was adapted to be followed for measurement instruments as recommended by Ludwine et al[15]. This systematic review was registered on the international prospective register of systematic reviews (PROSPERO) database (ID CRD42020206033).

Eligibility Criteria

Criteria for considering studies for inclusion in this systematic review for the primary and secondary objectives followed the PICO approach (population, intervention, comparison, outcome) and were agreed

by the authors (Tables 1 & 2).

Table 1
PICO Research strategy for systematic review (population, intervention, comparison, outcome) for primary objective.

PICO	Description
Population	Any person with CF who has been diagnosed by sweat testing, genotyping or both. Participants will be included irrespective of gender, age, or the presence of co-morbidities. People post-lung transplant were excluded.
Intervention	Any parallel or cross-over randomised controlled trial (RCT) investigating outcome measures of FEV_1 (spirometric tests) and sputum weight for airway clearance. Abstracts, case series and case studies were considered. All ACTs were eligible and included breathing exercises; hand held devices such as the acapella™, PEP or flutter™; HFCWO; postural drainage and percussion and non-invasive ventilation or exercise as ACT. Trials specifically testing pharmacotherapies were excluded.
Comparison	Trials were considered for inclusion if the author(s) compared any outcome measures with another outcome measure for measuring the effect of an ACT.
Outcomes	**Primary outcomes** - spirometric tests (e.g. FEV_1 or forced vital capacity (FVC) and sputum measures (e.g. sputum wet weight expectorated, dry weight, viscoelasticity) when used to evaluate the effect of ACT.
	Secondary outcomes - Other outcome measures such as exercise capacity tests, oxygen saturations, imaging, patient-reported outcome were included if used in conjunction with the primary outcomes.

Table 2
PICO Research strategy for systematic review (population, intervention, comparison, outcome) for secondary objective.

PICO	Description
Population	As per primary objective - Any person with CF who has been diagnosed by sweat testing, genotyping or both. Participants will be included irrespective of gender, age, or the presence of co-morbidities.
Intervention	Any parallel or cross-over randomised controlled trial (RCT) investigating outcome measures for airway clearance. Abstracts, case series and case studies were considered. All ACTs were eligible and included breathing exercises; hand held devices such as the acapella™, PEP or flutter™; HFCWO; postural drainage and percussion and non-invasive ventilation or exercise as ACT. Trials specifically testing pharmacotherapies were excluded.
Comparison	As per primary objective - Trials were considered for inclusion if the author(s) compared any outcome measures with another outcome measure for measuring the effect of an ACT.
Outcomes	**Primary outcomes** - Any outcome measures such as exercise capacity tests, oxygen saturations, imaging, patient-reported outcome measures and other physiological tests (e.g. multiple breath washout or impulse oscillometry) when used to evaluate the effect of ACT.

Literature Search Strategy

The review was conducted on the reporting of trials investigating the clinimetric properties of outcome measures used to assess the efficacy of airway clearance in people with CF. Our search strategy consisted of search terms (medical subject headings (MeSH) and text words) for each of the key PICO elements of the review: 1) the CF population; 2) the construct of airway clearance or chest physiotherapy; 3) all outcome measures used; 4) measurement properties (Tables 1& 2). This search strategy was adapted from a comprehensive search filter developed for PubMed by the Patient Reported Outcomes Measurement Group, University of Oxford which was recommended in the COSMIN methodology for systematic reviews of Patient-Reported Outcome Measures (PROMs) user manual[16] and published on the COSMIN website[17]. The medical librarian (RP) based at the X assisted development of our search strategy. Details of the search strategy can be found in the supplementary material.

In October 2020 searches were completed of the Cochrane Central Register of Controlled Trials (CENTRAL), PEDro (Physiotherapy Evidence Database), PubMed, MEDLINE and Science Direct databases without restrictions on year, publication status or language. Unpublished work was identified by searching Pediatric Pulmonology and the Journal of Cystic Fibrosis for the abstracts of two major CF conferences, the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. Separate searches of clinicaltrials.gov, ISRCTN registry and the WHO ICTRP databases were performed.

Literature search results were uploaded to the Covidence© software programme to allow collaboration among authors for screening abstracts, full-text review and risk of bias assessment.

Study selection

Search results were independently screened against the inclusion criteria based upon their title and abstract by two review authors (GS and MJ). Screening of the full text of studies that were not excluded based upon title and abstract was completed by the same authors (GS & MJ). A third author (NJS) was available to resolve any disagreement between the authors on study inclusion. Contacting authors to clarify trial details was attempted twice for two separate studies. The selection process and reasons for trial exclusion for the primary review objective are illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram at Fig. 2.

Screening for the secondary objective was completed following the same procedure and by the same authors. The selection process and reasons for trial exclusion for the secondary review objective are illustrated in the PRISMA flow diagram at Fig. 3.

Data collection process

Two review authors (GS & MJ) planned to assess the methodological quality of the selected studies and independently extract data using a standardised data collection form[18]. A third author (NJS) was

available to resolve any disagreements between authors.

The data extracted was planned to include: number of participants; participant characteristics; trial design (randomisation, allocations and concealment); details of the ACT intervention (type, duration, supervision, frequency, adherence); details of outcome measures used; publication status; financial support details. The authors planned to use the review software to manage and analyse this data (Covidence©). Results were planned to be grouped based upon type of outcome measure used. Subgroups of adult versus paediatric patients and stable versus exacerbating patients were planned.

Risk of bias in individual studies

The authors planned to independently assess study quality and risk of bias using the COSMIN risk of bias checklist[15, 19] including the following domains: cross-cultural validity; reliability; measurement error; criterion validity; construct validity and responsiveness. Studies were to be rated as very good, adequate, doubtful or inadequate for each of the domains. Each study's external validity would have been assessed based upon the details of study participants (e.g. mean age) and the study intervention.

Confidence in cumulative evidence

The authors planned to assess the quality of evidence for each outcome measure using the GRADE approach considering the studies over five domains (risk of bias; directness; consistency; precision and publication bias) to give the evidence a label of high, moderate, low or very low quality depending upon confidence in the estimate of effect.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Once it was apparent that no eligible studies existed for inclusion in this systematic review, the authors followed the guidance from the Cochrane Effective Practice and Organisation of Care (EPOC) resources for review authors in the reporting of empty reviews[12]and created a secondary objective to identify *any* outcome measures that had been clinimetrically evaluated for airway clearance assessment. The authors planned to use this information to suggest future work to evaluate outcome measures where insufficient evidence may be have identified.

Results

Primary objective results

The literature search identified a total of 187 studies or trials for screening, 186 were excluded after title and abstract screening was completed and one was subsequently excluded after full text review as it was a conference abstract reporting preliminary results[20] linked to one of the ongoing trials[21](Fig. 2). This resulted in there being no studies for further data extraction and analysis in this systematic review.

Of note, two ongoing studies were identified[22, 23] but publication of results of these trials is still pending. One of these trials is investigating the use of magnetic-resonance imaging (MRI) scanning compared to spirometry for ACT assessment[23], while the other compares the clinimetric properties of FEV_1, sputum weight, impulse oscillometry, lung clearance index derived from the multiple breath washout test and electrical impedance tomography when used for ACT assessment[22]. We excluded a conference abstract of preliminary results from this group[20] after full text review as it reported upon feasibility and reproducibility of OMS (LCI, IOS, EIT, FEV1) across two different visits, and did not report any pre- versus post-ACT data.

Secondary objective results

The 187 studies that were identified from the original literature search were then screened against the secondary objective. 181 studies were excluded as being irrelevant to the secondary objective, four were assessed by full text review and were subsequently excluded (Fig. 3). Reasons for exclusion were being a pilot study not an RCT[24] (one study); having the wrong study design as it investigated the effect of ACT upon LCI rather than if LCI could measure ACT effect[25] (one study); and being a conference abstract lacking detail[26] (one study) or reporting preliminary results only[20] (one study). Of note, the same two ongoing studies were identified as per the primary objective[22, 23], and one of these was linked to the conference abstract preliminary results report[20] which have been discussed after exclusion following full text review for the primary objective.

Two studies investigating LCI in the context of ACT were excluded after full text review[26, 27], the study design and reporting of these studies was such that they seemed to be investigating the impact of ACT on LCI measurements, rather than validating LCI for use as an outcome for ACT assessment. These studies reported conflicting results, with one study of 29 participants (mean age 21.8, range 7.3–43.7 years) showing that ACT may increase or decrease LCI due to ACT changing ventilation inhomogeneity[27], while the other study of 20 participants (age range 6–26 years, no mean given) showed no effect on LCI[26]. These studies indicate that the relationship between LCI and ACT warrants further investigation, and in the context of this review, requires specific study designs looking at the use of LCI to measure ACT effect.

The final excluded study was a pilot investigation into the use of hyperpolarised 3-Helium MRI scanning to assess the effects of ACT[24]; it was excluded due to a high risk of bias on randomisation whereby it could not be characterised as an RCT. The authors reported 3-Helium MRI scans as reproducible and highly sensitive to the effects of ACT but acknowledged their conclusions were limited as the study was underpowered due to small sample size.

Strengths And Limitations Of This Review

To the best of our knowledge, this is the first systematic review investigating clinimetric validation studies of outcome measures for ACT effect in the cystic fibrosis population. This review involved a thorough

search of several medical databases and clinical trials registries, based upon a comprehensive search strategy recommended by the specialist COSMIN group[17] and followed a clearly defined protocol which was published on the PROSPERO database (ID CRD42020206033).

“Airway clearance technique” is a broad term which encompasses many different techniques, from breathing exercises to mechanical adjuncts to exercise used as airway clearance. One limitation identified while undertaking this review was that while the literature search strategy (appendix 1) tried to include all terms for ACT, it is possible some may have been missed. A further limitation is that our search strategy focused on studies investigating the clinimetrics of outcome measures, and while a broad search strategy was created for this purpose following published guidance[16, 17] (appendix 1), there is a possibility that work looking at aspects of clinimetrics, but not specifically stating this within the title, abstract or keywords could have been missed. Furthermore, this review was purposely limited to evaluation of outcome measures for use with airway clearance, and so potential studies validating outcome measures for use other aspects of CF, which may be relevant to ACT, were not included.

Discussion

The aim of this review was to systematically assess the clinimetric properties of outcome measures when used to measure the effect of ACTs following the guidance described by the COSMIN group[17, 28]. No RCTs met the inclusion criteria for our primary or secondary objectives. This was not unexpected, as historical practice has been the adoption of outcome measures used in other aspects of CF care. Furthermore, several Cochrane reviews into ACTs have highlighted the need for more robust outcome measures in this area[6, 9].

The COSMIN group advocate that for effective outcome measurement it is essential that the construct being measured is clearly defined[10]. Based upon measurement theory[10, 29] airway clearance could be considered as a complex construct combining many different items which influence it (formative model) and which it influences (reflective model), for example, sputum production, breathlessness and ventilation inhomogeneity. In considering this, it could be concluded that assessing ACT by use of a single measure which may only reflect one item of the airway clearance construct could over simplify conclusions as to ACT effect. Ideally an outcome measure would be able to assess the construct of ACT as a whole.

From our literature search we note that many different outcome measures are being used in CF airway clearance research in addition to the traditional measures of FEV_1 and sputum weight. These include LCI derived from MBW tests, electrical impedance tomography and a variety of radiological techniques including 3-helium MRI. We acknowledge that within our excluded studies there was a pilot study investigating hyperpolarized 3-Helium MRI[24], and two studies investigating the effect of ACT upon LCI, suggesting preliminary work has been carried out in this area. While there were no accepted studies evaluating any measures, these outcomes may have been assessed for their clinimetric properties in regard to other aspects of CF, although identifying those validation studies was outside the scope of this review.

This review identified two ongoing studies[22, 23], which could suggest that the CF research community is trying to address the lack of robust ACT outcome measures. The results of these trials, which appear to be assessing the clinimetric properties of some of the emerging measures against historical outcomes (spirometry, LCI, plus two forms of MRI[23] and LCI, impulse oscillometry and electrical impedance compared to spirometry and sputum weight[22]) are urgently needed. Randomised controlled trials such as these are essential to enable clinicians and researchers to identify which outcome measures are appropriate to use for airway clearance assessment.

The demographics of the CF population is changing; there are now more adults than children with CF as people with CF live longer[1]. The development of cystic fibrosis transmembrane conductance regulator (CFTR) modulator medications, particularly the compound, elexacaftor/ tezacaftor/ ivacaftor (Kaftrio™/ Trikafta™) potentially suitable for 80–90% of the CF population[30], is likely to dramatically change the outlook for people with CF for the future[31]. These medications target the CF defect at the protein level, correcting abnormal ion transportation across cell membranes[32], thus preventing airway dehydration within the lungs. This limits the thick sticky mucus which traditionally has been a breeding ground for infection and a major cause of CF lung damage, leading to respiratory failure. It is thought that while early introduction of CFTR modulators will limit the development of CF lung disease, it will not be possible to correct established lung damage[31], and sputum will still be produced. While post-CFTR modulator sputum appears to be more fluid and easier to clear, ACTs to promote clearance and prevent lung infections may well remain part of daily management for many people with CF for the foreseeable future.

This positive advancement in CF management does provide a welcome problem when considering outcome measures for airway clearance assessment. Outcomes that have been used traditionally may not be relevant in this new post-CTFR modulator population, for example, sputum measures will not be helpful in people with minimal secretions, and spirometry may not be sensitive enough to pick up changes in a population with “normal” values[5]. A recent review into monitoring early stage lung disease in CF highlighted that the lack of measurable defects in spirometric values does not “indicate the absence of inflammation, infection and remodelling”[31]. Outcome measures used to assess people with CF, and other respiratory diseases, whether post-exacerbation, for monitoring or for the effects of ACT, need to be sensitive enough to pick up these early lung changes[33].

Furthermore, and essential for all CF healthcare professionals to consider, as the CF population continues to change, the recommendation of ‘daily ACT for all’ may change and the ability to thoroughly assess when ACT is required e.g. in times of exacerbation or declining respiratory status and equally, when it could be withdrawn, will be essential. LCI may be one measure which could be used for these assessments, having been shown to be sensitive enough to detect small changes in CF lungs[31]. However, although LCI has good clinimetric evidence as a long term outcome for use in the CF population[31, 34], validation is still needed for the use of LCI to measure short-term treatment effects[34], especially in relation to ACTs[25–27]. The use of LCI as an outcome may also be dependent upon disease stage, with emerging evidence that it may be impractical for those with severe lung disease due to

prolonged test duration[35]. People with advanced disease may also exhibit paradoxical LCI results due to changes in occluded lung units causing differences in the amount of communicating lung contributing to the MBW signal[36].

Similarly to this review, a recent systematic review investigating outcomes and endpoints used in CF pulmonary exacerbation studies also reported a wide range of outcomes used[37], with FEV_1 being the most common. The authors suggested the choice of outcomes may have historically been influenced by cost, available expertise and equipment[37]. This may also be the case for previous ACT trials, with spirometry and sputum weight being cheap and relatively easy[3]. The authors highlighted a need for a core outcome set for use in research into pulmonary exacerbations as described by the Core Outcome Measures in Effectiveness Trials (COMET) initiative[38] and emphasised that these endpoints should fulfil the desired characteristics of being both clinimetrically validated and clinically meaningful to people with CF[37], something which ACT research also requires.

Conclusion

Empty systematic reviews, i.e. reviews which find no eligible studies for inclusion to address an objective, are sometimes considered to offer no additional information to clinicians[39]. However, we argue that they serve to highlight the gaps in evidence for a particular area of interest[40]; we believe this is the case here. The assessment of the effect of ACTs is essential to enable effective management regimens for people with CF. The nature of airway clearance techniques, which can have multiple and differing effects on the individual, make them unique in measurement requirements, and using outcomes which have been assessed for other aspects of CF or other respiratory disease should not be recommended. Outcome measures should be clinimetrically assessed specifically in the context of ACTs and be clinically meaningful to people with CF. Identifying robust outcome measures which have had their clinimetric properties assessed for measuring ACT effect is essential. This systematic review highlights that there is a need for targeted RCTs that provide reliable, conclusive results to determine the most appropriate outcome measures to use for the assessment of ACT effect, both in the clinical and research settings.

Abbreviations

ACBT – Active Cycle of Breathing Techniques

ACTs – Airway clearance techniques

AD – Autogenic Drainage

CENTRAL – Cochrane Central Register of Controlled Trials

CF – Cystic Fibrosis

CFTR – Cystic Fibrosis transmembrane conductance regulator

COMET - Core Outcome Measures in Effectiveness Trials

COSMIN - COnsensus-based Standards for the selection of health status Measurement InstrumeNts

EPOC - Cochrane Effective Practice and Organisation of Care

FEV_1 – Forced expiratory volume in one second

FVC – Forced vital capacity

HFCWO – High Frequency Chest Wall Oscillation

ISRCTN - International standard randomised controlled trial number

LCI – Lung clearance index

MBW – Multiple breath washout

MeSH - Medical subject headings

MRI – Magnetic resonance imaging

OMs – Outcome measures

RCT – Randomised controlled trial

PeDRO - Physiotherapy Evidence Database

PEP – Positive expiratory pressure

PICO - Population, intervention, comparison, outcome

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PRISMA-P - Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PROMs – Patient reported outcome measures

PROSPERO - International prospective register of systematic reviews

WHO ICTRP – World Health Organisation's International Clinical Trials Registration Platform

Declarations

- **Ethics approval and consent to participate** – Not applicable
- **Consent for publication** – Not applicable

- **Availability of data and materials** - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- **Competing interests** - The authors declare that they have no competing interests.
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- **Authors' contributions** - GS: conceptualisation, methodology, validation, formal analysis, investigation, writing of original draft and revisions. MJ: conceptualisation, methodology, validation, formal analysis, investigation, writing of original draft and revisions, supervision. NJS, JCD, DB: conceptualisation, methodology, writing – review and editing, supervision. OU and SCC: writing – review and editing.
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- **REGISTRATION** –Registered on PROSPERO (ID CRD42020206033). Protocol can be accessed here.

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Appendix

Appendix 1 is not available with this version.

Figures

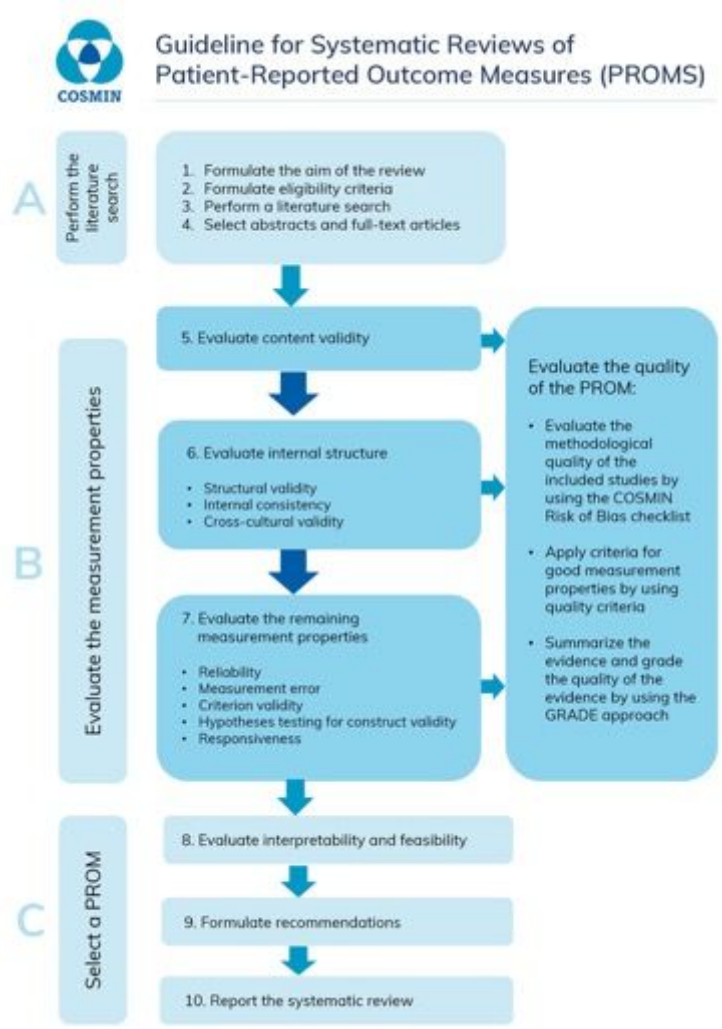

Figure 1

COSMIN 10 step procedure for systematic reviews of PROMs [14] (open-access permission from authors)

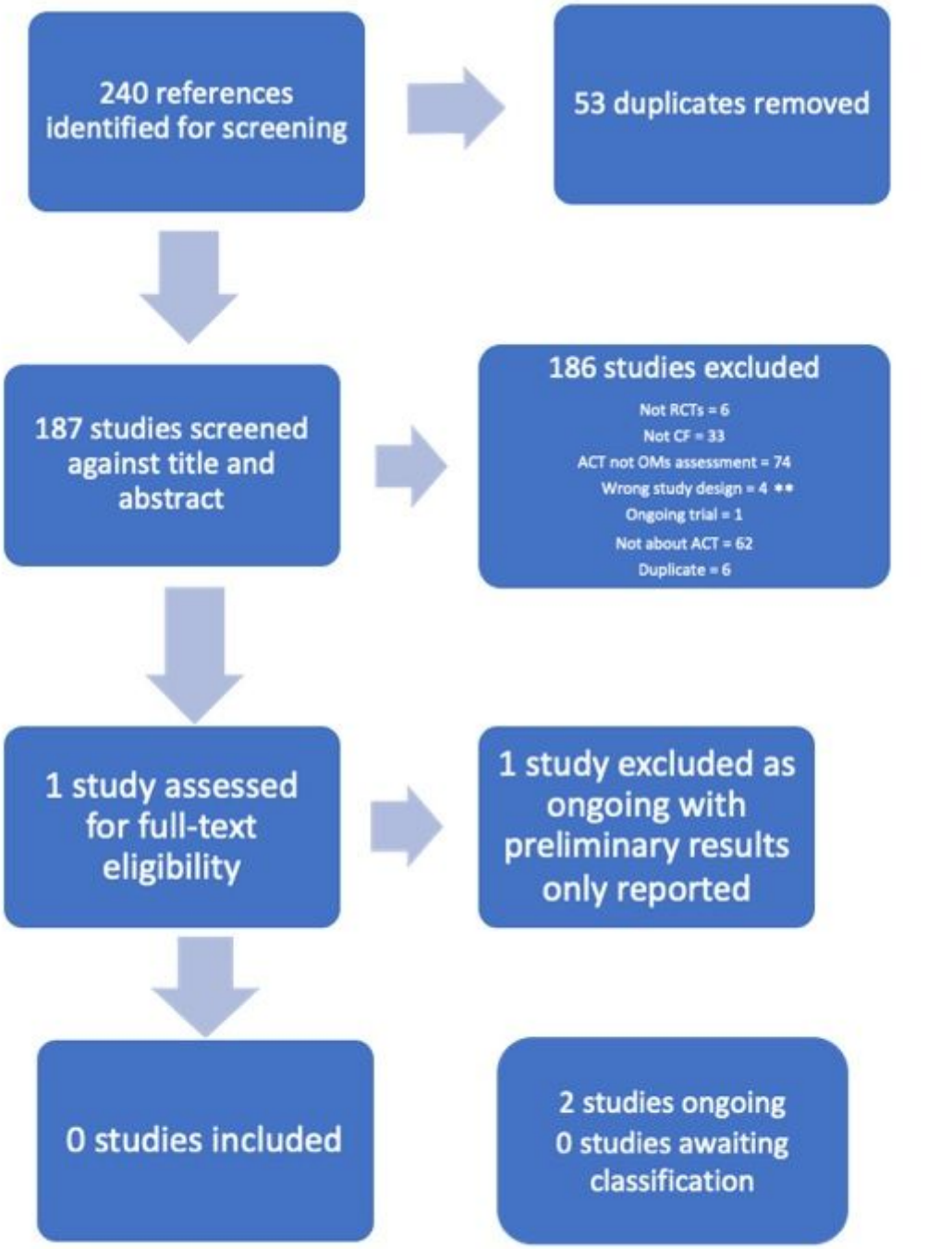

Figure 2

PRISMA flow diagram of the selection process for the primary review objective

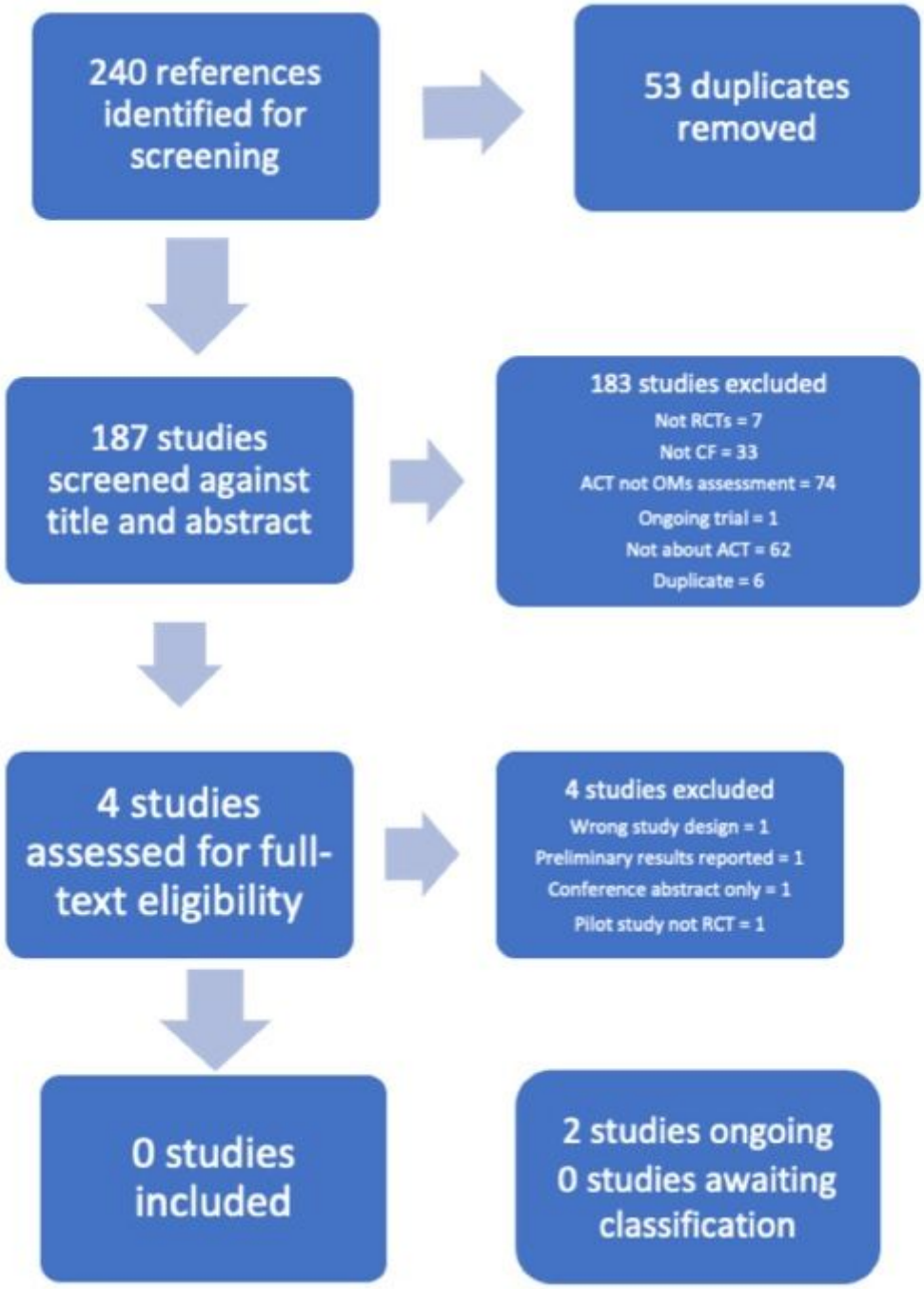

Figure 3

PRISMA flow diagram of the selection process for the secondary review objective

Supplementary Files

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