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Uptake of core outcome sets in paediatric clinical trials: a protocol

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ABSTRACT

Introduction A growing number of paediatric core outcome sets (COS) have been developed in the past 20 years. Previous studies have provided many useful insights into the uptake of COS. In addition to the awareness of COS among clinical trialists, the COS development process (especially patient participation) and the actions of the developers can promote COS uptake. However, the uptake of COS in paediatric clinical trials needs to be further explored. The aim of this study is to provide information on the rationale and use of paediatric COS in clinical trials, and to analyse in depth the awareness and views of COS developers and clinical trialists about the development and use of COS.

Methods and analysis We will include all paediatric COS identified in our previous systematic review and those subsequently included in the Core Outcome Measures in Effectiveness Trials (COMET) database. We will extract the target condition, population, intervention, list of core outcomes and the details of patient involvement. Next, we will search the Clinicaltrials.gov and WHO International Clinical Trials Registry Platform for trials on health conditions addressed by the identified COS. We will assess the comparability of the scopes in each COS-trial pair and determine for the outcomes in each clinical trial if they match exactly or generally, or if they do not match, with the outcomes of their respective COS. Finally, we will conduct a survey and semistructured interviews among COS developers and clinical trialists to examine their views.

Ethics and dissemination Ethical approval for the study has been granted by the ethics committee of the Institute of Health Data Science, Lanzhou University (No. HDS-202405–01). This study was registered on COMET (https://www.comet-initiative.org/Studies/Details/3122).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Core outcome sets (COS) can benefit the end users of trial results only if the clinical trials measure and report the core outcomes.
⇒ A growing number of paediatric COS have been developed in the past 20 years.
⇒ However, the uptake of COS and its potential facilitators and barriers in paediatrics have not yet been thoroughly studied.

WHAT THIS STUDY HOPES TO ADD

⇒ This study aims to describe the use of COS in paediatric clinical trials and evaluate the overlap of the scope between existing COS and paediatric clinical trials.
⇒ Based on the results of the use of paediatric COS, the study will explore the views of COS developers on the improvement of COS development for paediatric health conditions, and actions to improve uptake of COS by clinical trialists.
⇒ We will also explore clinical trialists' knowledge, perceptions and views on use of COS in choosing outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings will provide an overview of the uptake of paediatric COS and the potential facilitators and barriers to improve the use of COS in paediatric clinical trials.

INTRODUCTION

A core outcome set (COS) is a standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials on a given topic of health or healthcare.[1] Identifying and using COS will facilitate evidence synthesis, increase comparability across studies, reduce selective reporting of outcomes and increase the relevance of the results to stakeholders.[2 3]

More than 20 years has passed since the publication of the first study to guide the selection of outcomes for paediatric clinical trials.[4] Since then, a growing number of paediatric COS have been developed, especially after the Core Outcome Measures in Effectiveness Trials (COMET) Initiative was launched in 2010 to provide more resources. COS can benefit the end users of trial results only if the clinical trials measure and report the core outcomes.[5]

Previous research has shown that COS uptake is low in most clinical research areas.[6 7] Reasons for low uptake include a lack of knowledge among clinical trialists about the perceived importance of COS and identifying COS,[5 8] and concerns about measuring COS (including perceived patient burden,[9] and the belief that COS are limiting and often contain too many outcomes[8]). The COS

development process and the actions of the developers are also important factors influencing the use of COS. Such factors include the involvement of patients and representatives of all specialties that will use the COS,[9] and actions to promote uptake that go beyond traditional dissemination methods.[5] However, studies assessing the uptake of COS have mainly focused on clinical research in adults,[6] and only a few studies have addressed the uptake of paediatric COS specifically.[10–12]

Our proposed study aims to (1) describe the use of COS in paediatric clinical trials; (2) explore the views of COS developers on the improvement of COS development for paediatric health conditions, and actions to improve uptake of COS by clinical trialists; and (3) explore clinical trialists' knowledge, perceptions and views on the use of COS in choosing outcomes.

Methods and analysis

Review and comparison of paediatric COS and clinical trials

Identification of COS

We will include all the paediatric COS identified in our previous systematic review[4] and those subsequently included in the COMET database using the following inclusion criteria.

1. The target population consists fully or partly of children (younger than 18 years). If the lower age limit is 16 years or above, we will check whether the COS primarily targets adults; if so, we will exclude it.
2. The study type is COS for clinical trials.
3. Children and/or their parents or other caregivers were involved in the development of the COS.

Identification of clinical trials

We will search Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform for trials on health conditions addressed by the included COS and remove duplicates. We will use the same categoriqation of health conditions as the registries and determine for each COS the corresponding conditions to link the COS with the trials.

We will include trials that fulfil the following criteria: (1) the target population consists fully or partly of children (younger than 18 years); (2) the trial examines the effectiveness of an intervention compared with standard care or another comparator; and (3) time of trial commencement, defined as the date of trial registration, protocol publication or start of participant recruitment whichever is the earliest, is later than the date the COS was published; and (4) randomised and non-randomised trials without any restrictions on sample size, intervention type or trial design.

We will exclude trials that (1) assessed the effectiveness of an intervention on comorbidities or complications of the health condition; (2) assessed the mechanisms or development of biomarkers for the effect of the intervention; (3) were pilot or feasibility studies; or (4) were secondary analyses of data from previously published clinical trials.

Assessing overlap in scope of topics between clinical trials and COS

The Core Outcome Set-STAndards for Development[2] identifies the research or practice setting(s), the health condition(s), the population(s) and the intervention(s) as the scopes of the COS. We will select the COS and clinical trials to be included according to their target setting and health condition. We will use a previously developed framework,[13] which contains the population and intervention, to assess the comparability of the scopes in each COS-trial pair (table 1). Sixteen scenarios are possible, which can be further categorised into the following three main cases:

1. The COS is *very likely to be relevant* if its scope is at least as broad as the outcome set of the trial in terms of both the population and the intervention (scenarios 'f', 'g', 'j' and 'k').
2. The COS *may be relevant* in scenarios in which the COS is narrower than the clinical trial in terms of the population, intervention or both (scenarios 'a', 'b', 'c', 'e' and 'i') or in which the clinical trial and COS target different subgroups of the population (scenarios 'm', 'n' and 'o'). While all assessments of overlap in scope between a given clinical trial and a given COS should involve clinical expertise, this is particularly important in scenarios that involve different subgroups of the population (scenarios 'm', 'n' and 'o').

Table 1 The framework for assessing overlap in scope between a COS and a clinical trial

		Intervention			
		COS is narrower	Exact match	COS is broader	Different but related intervention
Population	COS is narrower	A	B	C	D
	Exact match	E	F	G	H
	COS is broader	I	J	K	L
	Different population subgroup*	M	N	O	P

White cells=very likely to be relevant; light grey cells=may be relevant; dark grey cells=unlikely to be relevant.
*Requires careful clinical consideration

3. The COS is *unlikely to be relevant* in scenarios in which the clinical trial and the COS describe different (but related) interventions (scenarios 'd', 'h', 'l' and 'p').

Matching of COS and clinical trials

We will include COS-trial pairs that fulfil all of the following conditions:

1. The pair is judged as either 'very likely relevant' (white cells) and 'may be relevant' (light grey cells) as shown in table 1;
2. The number of relevant clinical trials on the topic is at least 40. If the number is too small, the comparison of the COS and the outcomes of the trials is not meaningful. According to the results of a preliminary search on Clinicaltrials.gov, we found that the number of potentially relevant clinical trials for most conditions was small, with only 7 eligible COS having at least 50 corresponding trials. By decreasing the limit to 40, we were able to find 3 additional COS with sufficiently many trials; if we decreased it to 30, there were no more COS compared with 40. Therefore, we selected 40 as the minimum number of trial; and
3. If two or more COS developed for same condition meet above two criteria, we will selected the COS according to the following criteria applied hierarchically: (1) both Delphi and consensus meeting were used in the consensus process; (2) higher ratio of children/parents to healthcare professionals in the consensus process; (3) children themselves (instead of their parents only) participated in the process, if applicable; and (4) children/parents from multiple regions were involved.

Matching of outcomes between the COS and clinical trials

In the comparison of the COS and the outcomes of the trial, we will include all primary, secondary and exploratory outcomes mentioned in the trial registry. Three situations are possible:[7 13]

1. *Exact match*: the outcomes match exactly including the use of the same or synonymous/equivalent terms (eg, 'overall survival' and 'all-cause mortality');
2. *General match*: the outcomes match on a general level, including one outcome being part of another (eg, 'functioning' and 'emotional functioning'; 'disease activity' and 'joint damage') or outcomes being to large extent overlapping (eg, 'drug adherence' and 'intake of any treatment');
3. *Non-matches*.

For each pair of outcomes that is a general match, we will also assess which of the two outcomes, the core outcome or the trial outcome, is broader. When this cannot be determined, we will not make an assessment about the comparative breadth of the outcomes.

Data extraction

The following data will be extracted for each COS:

1. Characteristics of the COS: first author, title, country (first author), category of the condition, name of the condition, date of publication, age range of target population, nature of intervention, list of core outcomes.
2. Details of children's/parents' participation: (1) countries/regions of patients involved in development, specific development process children/parents were involved in (forming the outcome list, rating the importance of outcomes); (2) methods of forming the outcome list by involving the children's/parents' view (such as interviews, focus group discussions), types of patient representatives involved in forming the list (such as children, parents, or both), number of children/parents, age range of children (if applicable); and (3) methods of rating the importance of outcomes considering the patient's view (such as Delphi, consensus meeting), types of patient representatives contributing in the rating of outcome importance, total number of participants, number of children/parents, age range of children, country/region of children/parents.

From clinical trials, the following data will be extracted:

1. Basic information: first author, study title, link to the study protocol or trial registration;
2. Characteristics of the trial: condition(s), type of intervention, age range of target population, time of trial commencement (date of trial registration, protocol publication, or start of participant recruitment whichever is the earliest), phase, study design, samples, type of funding, list of outcomes;
3. Uptake of COS details: whether the outcomes of the COS were used (partially or completely); if used, list the primary and secondary outcomes separately.

Data analysis

Frequencies, percentages and medians with IQRs will be used to describe the characteristics of the included clinical trials and COS. We will calculate the time lapse between the date of the COS' publication and the time of trial commencement; the distribution of the 16 scenarios of overlap between COS and clinical trials as stated in table 1; for the outcomes in each COS that are exact matches, general matches and non-matches with outcomes in each clinical trial; the changes in proportions of exact matches or general matches between the COS and the corresponding trials over time since the publication of the COS.

Survey and semistructured interviews among COS developers and clinical trialists

The survey participants are provided a summary of all quantitative results achieved in the project so far, together with other relevant information. Then, questionnaires with a mixture of multiple-choice and open-ended questions will be sent to paediatric COS developers and clinical trialists. The participants will need to answer to between 11 and 20 questions, inclusive of background information, which is expected to take about 10–15 min. During the communication, we also ask the participants if they would be willing to be individually

interviewed in person or online. For COS developers, we aim to examine their views on barriers and facilitators to improve the development process of COS, and on actions to improve uptake of COS by clinical trialists. Among clinical trialist, we aim to examine their views on the knowledge, perceptions and use of COS in relation to choosing outcomes; in addition, we also plan to explore the ideas about improving the development process of COS among investigators who are familiar with COS.

Participants

Lead developers (first and corresponding authors) of the paediatric COS and lead authors of clinical trialists identified in this study will be invited to participate. If the lead developers or authors do not respond, other authors of the respective study will be approached. For the survey, since there is no quantitative hypothesis we aim to prove, we have made no formal sample size calculation. For the interviews, we will invite survey respondents who agreed to be interviewed, and continue until no more substantial new information can be gained.[14]

Data collection

Potential participants will be contacted by email with an initial invitation that includes a detailed description of the purpose of this study. If no response is received, a reminder email will be sent 3 weeks later. In case of 'out-of-office' responses, we will follow up with the potential participant on an individual basis. Before commencing the online survey, the participants will be required to confirm their consent by email.

Those who agree to participate in a semistructured interview will be interviewed at a time that suits them. Each interview will last at least 30 min and will be audio-recorded so that any ambiguities can be clarified.[15]

The survey questions and interview topic guide are informed by previous studies[6 9 16 17] and are presented in the online supplemental file.

Data analysis

Results from the survey of COS developers and trialists will be analysed using descriptive methods. Answers to dichotomous questions will be presented as frequencies and percentages. Open-ended questions and the developers' and clinical trialists' views on the development and uptake of COS will be analysed using a thematic analysis approach according to a framework consisting of the following steps:[18] (1) familiarising ourselves with the data; (2) generating initial codes; (3) generating or developing draft themes; (4) reviewing the identified themes; and (5) defining and naming the themes.

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Competing interests No, there are no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Review Committee of Lanzhou University Institute of Health Data Science, China (NO. HDS-202405-01). Participants gave informed consent to participate in the study before taking part.

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