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ORIGINAL ARTICLE

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Abstract

Objectives: To examine current practices in late-phase trials published in major medical journals and examine trialists' views about core outcome set (COS) use.

Study Design and Setting: A sequential multi-methods study was conducted. We examined late-phase trials published between October 2019 and March 2020 in *JAMA, NEJM, The Lancet, BMJ*, and *Annals of Internal Medicine*. The COMET database was searched for COS potentially relevant to trials not reporting using a COS; overlap of trial and COS outcomes was examined. An online survey examined awareness of, and decisions to search for and use a COS.

Results: Ninety-five trials were examined; 93 (98%) did not report using a COS. Relevant COS were identified for 31 trials (33%). Core outcomes were measured in 9 (23%) studies; all trials measured at least one core outcome. Thirty-one trialists (33%) completed our

Conflicts of interest: Paula Williamson chairs the COMET Initiative Management Group. Sarah Gorst is the COMET Initiative Project Coordinator. Caroline B Terwee is a member of the COSMIN steering committee. All study authors are members of the MRC-NIHR Trials Methodology Research Partnership Outcomes Working Group, have been involved in COS research previously, and have expressed a preference for COS use in past papers.

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survey. The most common barrier to COS use was trialist's own outcome preferences and choice (68%). The most common perceived facilitator was awareness and knowledge about COS (90%).

Conclusion: COS use in this cohort of trials was low, even when relevant COS were available. Increased use of COS in clinical trials can improve evaluation of intervention effects and evidence synthesis and reduce research waste.

Key Words: Core outcome sets; Trials; Trial outcomes; Health outcomes; Medical Journals; Outcome reporting

What is new?

Key findings

- Ninety-eight percent of trials did not report using core outcome sets, even when relevant core outcome sets were available.
- Trialist reported barriers to core outcome set use included preference to choose their own outcomes and poor knowledge about existence of core outcome sets.
- Trialist reported facilitators to core outcome set use included understanding of what core outcome sets are and their perceived importance.

What this adds to what was known?

- Core outcome sets are not typically used and/or reported in late phase trials published in major medical journals.

What is the implication and what should change now?

- There is scope for increased uptake of COS in clinical trials to improve evaluation of intervention effects and evidence syntheses, reduce research waste, and potentially improve patient care.

1. Introduction

Appropriate choice and reporting of outcomes in clinical trials are essential for evaluating and synthesizing evidence about intervention effects and informing clinical practice [1,2]. A core outcome set (COS) is a standardized set of outcomes, agreed upon by stakeholders, that should be the minimum outcomes measured, and reported in all trials in particular health areas [3]. COS are not necessarily the only outcomes to be measured, other outcomes can be used, they are instead the minimum that should be included [3]. Using COS in clinical trials can improve intervention evaluation and evidence syntheses [3]. COS use can also minimize issues in trials, including selective outcome reporting [4], outcome heterogeneity [5–7], and research waste [8], while enhancing research transparency [3,9]. Integrating stakeholder views in COS development ensures inclusion of outcomes of clinical importance and relevance to stakeholders [10], including patients, which increases the likelihood that COS will be used in trials [8,10,11].

At of the end of 2019, 370 COS studies were published, with at least 200 additional COS being developed, for a range of health areas [12]. Reviews of COS uptake in trials indicate varying, though generally low, rates of use [13]. A 2020 analysis of Cochrane systematic reviews found that COS were reported to inform outcome choice in just 7% of reviews [14]. Analysis of funding applications submitted to the National Institute for Health Research Technology Assessment (NIHR HTA) found that 38% of applicants searched for a COS to inform outcome choice [13]. Similarly, in a survey of trialists with trials registered on the International Standard Randomized Controlled Trial Number (ISRCTN) Trial repository, most trialists had not been involved in a trial that included a COS [15]. Of those trialists who had used a COS, in most instances not all COS outcomes were used [15].

To date, examinations have been conducted on uptake of COS for individual COS use in specific health areas [16], funding applications [13], and trial registrations [15]. We are not aware of an examination of COS uptake in a general unselected cohort of published clinical trials. Similarly, we are not aware of studies examining barriers or facilitators of COS use among trialists of published trials. It is important to examine COS use across a range of clinical trials and trialists to determine if, how, and why COS, developed for a range of health topics, are being used or not across these diverse areas. This information is essential to inform future uptake and reporting of COS in clinical trials, which can improve examination and synthesis of intervention effects, reduce heterogeneity and selective outcome reporting, and may lead to better patient care.

Aims:

1) To examine current practices in late phase trials published in major medical journals, in relation to COS use in choosing trial outcomes.
2) To examine trialists views on use of COS in choosing trial outcomes.

2. Methods

The protocol for this study is published [17]. Methods are presented here in brief; changes to the protocol are included in Supplementary File 1. Ethical approval was

obtained from the University College Cork Social Research Ethics Committee (2020-137).

2.1. Identification of trials

We reviewed five major medical journals to identify late phase trials: *Journal of the American Medical Association (JAMA), New England Journal of Medicine, The Lancet, BMJ*, and *Annals of Internal Medicine*. These journals were selected because they are general medical journals widely recognized as publishing high quality, robust clinical research. Journal websites were searched across a 6-month period; October 2019–March 2020. Late phase trials were defined as randomized studies examining effectiveness of interventions typically in relation to standard care or another comparator. Late phase trials are typically classified as phase III or phase IV in pharmacological trials; the term late phase is used herein because this classification is not generally used in non-pharmacological trials. Late phase trials utilizing any design (e.g., parallel, factorial) and any level of randomization (e.g., individual or cluster) were eligible. There were no restrictions for intervention type, health area, or sample size. Two reviewers (KMS & VS) independently screened identified trial publications against eligibility criteria. Discrepancies were resolved by discussion or resolution by a third reviewer (PRW).

2.2. Data extraction

A standardized data extraction form was pilot tested on five trial publications by KMS, PRW, JJK, IJS, VS, FQ, KM, SP, and subsequently refined (see Supplementary File 2). Data were independently extracted from remaining trial publications by eight reviewer pairs, each randomly allocated to 11 or 12 trials. Data extracted included study details, intervention details, whether and to what extent a COS was mentioned in the trial publication, whether COS outcomes were used, and rationale for choice of outcomes used (if any). Where a COS was used, reviewers extracted data on the COS, including number of COS outcomes used, and whether the primary outcome for the trial was a COS outcome. Reviewers also identified corresponding trial protocols and/or registrations via details provided in trial publications or online searches. Data were extracted on date of protocol publication/trial registration and whether a COS was mentioned in either the protocol or any version of the trial registration.

2.3. Identification of potentially relevant COS

For trials not reporting COS use, we searched for whether a COS existed that could have been used at time of trial commencement, which was considered the earliest date from either trial registration, protocol publication, or commencement of participant recruitment. We searched the online, regularly updated Core Outcome Measures in Effectiveness Trials (COMET) Initiative database (www.comet-initiative.org) for potentially relevant published COS. Data extracted included COS title, and eligible population and intervention details. Reviewers also evaluated whether the COS population and intervention were narrower, broader, different from, or an exact match with the trial population and intervention, respectively; see Supplementary File 3. Reviewers conducted data extraction and COS identification independently and reached consensus before returning this for checking by KMS and PRW. Identified COS were evaluated by KMS and PRW for relevance to trials, using a framework for assessing the scope of COS, with COS rated as either 'very likely to be relevant,' 'may apply,' and 'unlikely to apply' [18].

2.4. Assessing overlap between trial and COS outcomes

For trials not reporting COS use and for which a potentially relevant COS was identified, outcomes reported in the trial and COS were compared. The list of trial outcomes was extracted from the trial publication methods section and/or trial protocol. If the trial publication stated that outcomes originally included in the protocol were later eliminated/changed, only updated outcome information was extracted. Exact and partial outcome matches were identified. Exact matches include synonymous terms for a given outcome (e.g., survival, death); partial matches could include a subset of each other (e.g., "functioning" vs. "emotional functioning") or potential overlap (e.g., "drug adherence" and "intake of any treatment"). This was conducted by one reviewer with expertise in outcome matching (SD) and checked by KMS.

2.5. Survey of trialists

We sent a survey to corresponding authors of all identified trials. When corresponding authors could not be contacted, another trial author was approached. Survey invitation emails included an information leaflet, online survey link, and details of identified COS where relevant. Where more than one potentially relevant COS was identified, a maximum of two COS was sent to each trialist. Choice of these COS was based on scope, relevance, and recency, as discussed and decided by KMS, PRW, and the reviewer-pair for that trial.

The survey included closed and open-ended questions examining trialists' awareness of COS; searching for, identification and use of COS; perceived barriers and facilitators to COS use; and perceived challenges and benefits of COS use where a COS was used. If a COS was not used, trialists were asked about reasons for outcome choices. If we identified potentially relevant COS for trials, trialists were asked whether they thought the identified COS was a good fit for their trial. Five survey versions were developed; questions differed based on COS use in identified

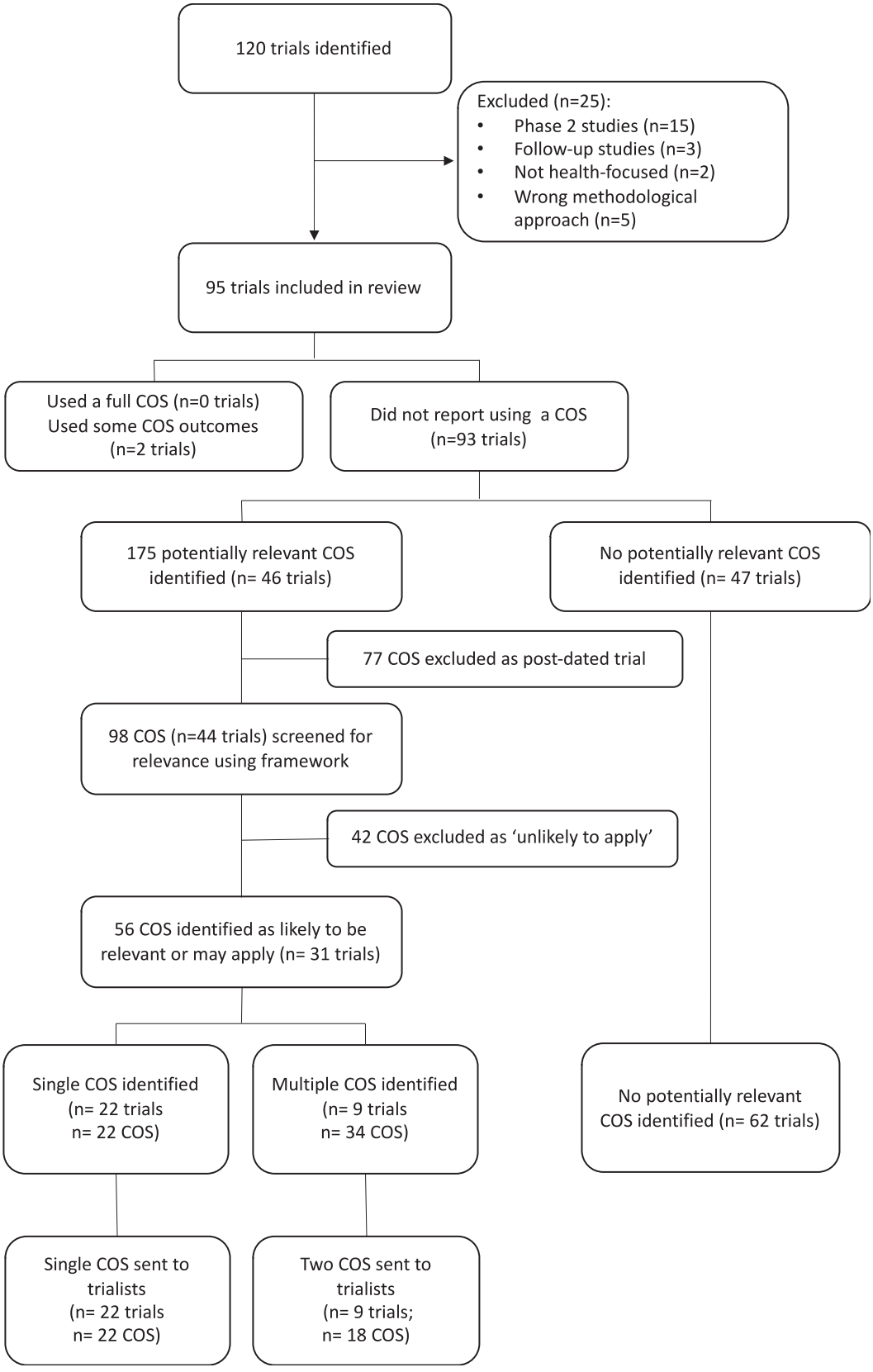

Fig. 1. Flow diagram of trial and COS identification, and trialist survey.

trials, and identification of potentially relevant COS. See Supplementary File 4.

2.6. Analysis

Data extracted from trials and survey results are presented descriptively. The main parameters of interest were the numbers and percentage of trials using a COS (including extent of COS use) and that could have used a COS. Secondary parameters were concordance between outcomes used in trials and identified COS, and trialists' awareness of, and decisions to search for and use a COS. Open-ended survey questions were analyzed using content analysis by qualitatively coding responses and grouping codes based on similarity. Closed and open-ended question responses were subsequently grouped into overarching categories based on similarity. Findings are presented narratively and in tabular format. Data are available from the corresponding author on request.

3. Results

One-hundred-and-twenty potentially relevant trials were identified, and 95 trials were included, see Fig. 1. Most trials commenced in 2010 of 2011 (56%), included pharmacological interventions (56%), and studied adult populations (75%). Fifteen trials (16%) included explicit statements describing how outcomes were chosen.

No trial reported using all COS outcomes. Two trials (2%) used some but not all COS outcomes; one of these used a COS outcome as the primary trial outcome. The two trials reporting using COS mentioned the COS in the trial protocol and/or registration but not in the final trial publication. Most trials ($n = 93$; 97%) did not report using a COS. See Table 1.

3.1. Identification of potentially relevant COS

Of 93 trials that did not report using any COS outcomes, we initially identified 175 potentially relevant COS for 46 trials. Seventy-seven COS were excluded because they were published after trial commencement. Forty-two additional COS were evaluated as 'unlikely to apply' based on population and intervention scope [18]. Fifty-six potentially relevant COS were therefore identified for 31 trials. Of these, one relevant COS was identified for 22 trials; multiple COS were identified for 9 trials. COS were not identified for 62 trials. See Table 2, Fig. 1.

3.2. Trial and COS outcome overlap

Examination of overlap between outcomes in trials that did not report using a COS and identified COS, found that 9 (23%) of 39 trial/COS pairs (relating to 31 trials) included all core outcomes (based on exact or partial outcome match). All trial/COS pairs included at least one (ex-

Table 1. Characteristics of included trials ($n = 95$) including COS use

	***n* (%) trials**
Trial year of publication	
2020	37 (39%)
2019	58 (61%)
Year of trial commencement[a]	
2005 or earlier	4 (4 %)
2006–2010	10 (11%)
2010–2011	53 (56%)
2016–2019	28 (29%)
Trial disease categories	
Blood disorders	3 (3%)
Cancer	14 (15%)
Child health	1 (1%)
Ear, nose and throat	1 (1%)
Endocrine and metabolic	4 (4%)
Eyes and vision	3 (3%)
Gastroenterology	6 (6%)
Genetic disorders	2 (2%)
Gynecology	2 (2%)
Heart and circulation	10 (11%)
Infectious diseases	10 (11%)
Kidney disease	1 (1%)
Lungs and airways	3 (3%)
Neurology	8 (9%)
Orthopedics and trauma	4 (4%)
Pregnancy & Childbirth	8 (9%)
Rheumatology	5 (5%)
Skin	3 (3%)
Wounds	1 (1%)
Other	6 (6%)
Trial intervention type	
Surgical	14 (15%)
Pharmacological	54 (57%)
Multicomponent	5 (5%)
Other	21 (22%)
Dietary/supplementation	5(5%)
Obstetric	4(4%)
Radiation therapy	3 (3%)
Blood transfusion	2 (2%)
Home/community care	2 (2%)
Healthcare systems	2 (2%)
Functional bracing	1 (1%)
Emollient use	1 (1%)
Acupuncture	1 (1%)
Trial population	
Adults	71 (75%)
Children	9 (9%)
Both adults and children	14 (15%)

(*continued on next page*)

Table 1 (*continued*)

	n **(%) trials**
Not reported	1 (1%)
Statement of trial outcome choice[b]	
Outcomes were used in previous examinations	6 (40%)
Based on regulatory body guidance	3 (20%)
The outcomes are considered well validated	3 (20%)
Outcomes are associated with and/or are proximal markers of other outcomes of interest	3 (20%)
Based on patient centeredness	2 (13%)
Consensus decision among clinical trial investigators	1 (7%)
Statistical rationale (i.e., power calculation)	1 (7%)
COS use	
Full COS was used	0
Some COS outcomes used	2 (2.1%)
Primary outcome was from COS	1 (1.0%)
No COS use reported	93 (97.9%)

[a] As indicated by earliest date from protocol publication, trial registration or commencement of participant recruitment.
[b] Some trial publications provided more than one justification for outcome choice.

act or partial match) core outcome. See Supplementary File 5.

3.3. Trialist survey

Trialists for 31 of 95 trials (33%) completed the survey, including a trialist of one of the two trials that used a COS. This trialist reported that they identified the COS based on their involvement in COS development; they chose to use a COS "*to enable future trials to be combined in a meta-analysis.*" They reported using only some COS outcomes to address the trial focus and noted a challenge of including one of the core outcomes was the need for training in how to assess that outcome.

Among 30 trialists not reporting COS use, 15 (50%) reported searching for a COS before the trial via literature searches (87%) and/or speaking with colleagues (80%); 4 (27%) reported searching the COMET database. A COS was identified in 6 of these 15 searches (40%). See Table 3. Reasons for not using the identified COS were that it was "*for a different population,*" "*had not been validated,*" "*outcomes were rare so a composite outcome had to be used,*" and "*the primary endpoints were those recommended by FDA.*"

Of the seven trialists made aware of an identified COS and who completed the survey, four thought the identified COS was not relevant. Reasons included that the COS was missing outcomes the trialists used in a composite outcome; the focus of the COS and trial interventions differed; outcome guidance had been updated by relevant regulatory and professional bodies; pragmatic reasons, including cost; lack of familiarity with outcomes; and overlap between COS outcomes and those already included in the trial.

Table 2. Characteristics of identified COS ($n = 39$) for 93 trials not reporting COS use

	n **(%) trials**
COS identification	
Relevant COS not identified	62 (66.7%)
Relevant COS identified	31 (33.3%)
Single COS identified	22 (23.7%)
Multiple COS identified	9 (9.7%)
Identified COS characteristics ($n = 39$ COS)	
COS year of publication	
2005 or earlier	11 (28.2%)
2006–2010	10 (25.6%)
2010–2011	14 (35.9%)
2016–2019	4 (10.3%)
COS disease category	
Cancer	8 (20.5%)
Heart and circulation	6 (15.4%)
Rheumatology	4 (10.2%)
Orthopedics and trauma	4 (10.2%)
Pregnancy and childbirth	3 (7.7%)
Infectious diseases	2 (5.1%)
Endocrine and metabolic	2 (5.1%)
Neurology	2 (5.1%)
Lungs and airways	2 (5.1%)
Stroke	1 (2.6%)
Ear, nose, and throat	1 (2.6%)
Genetic disorders	1 (2.6%)
Infectious disease	1 (2.6%)
Intensive care	1 (2.6%)
Gastroenterology	1 (2.6%)
Number of COS outcomes	
Median	7
Inter quartile range	(4, 11)
Range	(1, 48)
Mean	8.49
Standard deviation	7.41

The most frequently endorsed perceived barriers related to using a COS in trials included researcher outcome preference and choice (77%), knowledge about COS (61%), and measurement issues (61%). The most frequently endorsed perceived facilitators were awareness and knowledge about COS (90%) and positive perceptions of COS (84%). See Table 4.

The most frequently endorsed sources for identifying non-COS outcomes were outcomes used in previous trials (84%) and practitioner opinion (65%). Other sources in-

Table 3. Survey responses from trialists ($n = 30$) not reporting use of a COS

	***N* (%)**
Searched for COS before trial	15 (50%)
Sources used to identify COS before trial ($n = 15$ trialists)	
COMET database	4 (27%)
Literature search	13 (87%)
Discussion with colleagues	12 (80%)
Discussions with subject experts, study advisory committee	1(7%)
NIH NINDS website	1(7%)
Worked on the guidelines, endpoints selected based on FDA guidance	1(7%)
Chairing working group developing a COS	1(7%)
COS was identified by trialists before trial but not used ($n = 15$ trialists)	6 (40%)
COS identified in review and sent to trialists was relevant ($n = 7$ trialists)	
Yes	3 (43%)
No	4 (57%)

COMET, Core Outcome Measures in Effectiveness Trials; COS, Core outcome set; FDA, Food and Drug Administration; NIH NINDS, National Institutes of Health National Institute of Neurological Disorders and Stroke

cluded recommendations from professional bodies (42%), feasibility or pilot studies (42%), and/or systematic reviews (42%). See Supplementary File 6.

4. Discussion

This study demonstrates that most 95 trials published recently in major medical journals did not use a COS even when relevant COS were available. All trials included some COS outcomes, however. Our survey of trialists revealed trialist's own preferences for outcomes and poor knowledge about the existence of COS as barriers to COS use. Perceived facilitators included understanding of what COS are, perceived importance of COS, and recommendations from funders and professional bodies to use COS.

Identification of low COS use in this cohort of trials is consistent with previous examinations [13,14]. One possible explanation may be low levels of knowledge about the existence and value of COS [15]. This is reflected in survey responses indicating that knowledge about COS is important for COS use. Similarly, even among trialists who reported searching for a COS before conducting their trial, few reported searching the COMET database, indicating poor awareness about available resources that can support COS use in trials.

Our search of the COMET database indicated that potentially relevant COS existed for one-third of included trials. This is surprising because an analysis of COS use in recently published systematic reviews identified relevant COS for 54% of reviews [18]. This suggests there is scope for development of COS in topics actively being studied in clinical trials. For instance, we did not identify relevant COS for trials related to blood, eyes, skin, or genetic disorders. While existing COS may not be relevant based on scope of the population and/or intervention examined in the trial [18], there may still be value in reviewing core outcomes in areas related, albeit not directly, for aligned/relevant outcomes.

That all trials used at least some outcomes from identified COS, irrespective of whether trialists reported the outcomes as such, highlights the relevance of COS for clinical trials. This was also highlighted by some survey responses that trialists already measured the most important core outcomes. The use of COS that have been developed and agreed upon by key stakeholder groups, including trialists, patients and other decision-makers, ensures that outcomes used are relevant, important, and meaningful to those who will use/benefit from the research [3,10]. However, it is important that COS developers ensure stakeholders are representative of target populations to maximize COS usefulness.

The COMET guidelines recommend measuring and reporting all COS outcomes as the minimum in trials [3]. A previous survey of trialists with a trial registered on the ISRCTN repository found that fewer than half of respondents who had used a COS in a trial reported including all COS outcomes [15]. In addition to poor COS knowledge, lack of full COS use and/or reporting in the current study may be due to trialists perceiving identified COS as not relevant or valid for use. However, the low numbers of trialists who searched for potentially relevant COS indicates that COS searching and evaluation are not being conducted as a minimum during protocol development. Further, few trialists in the current study provided justifications for outcome choice. Though current trial reporting guidelines do not require outcome choice justification, work is ongoing to develop a reporting standard for clinical trials to improve outcome reporting in trials [19].

Additional barriers to COS use and reporting in the current study related to poor knowledge about what COS are, how to identify and use them, and the availability of guidelines and resources for COS use. This highlights the need

Table 4. Barriers and facilitators to core outcome set use reported by trialists ($n = 31$)

Barriers to core outcome set use in trials	N(%)
Researcher outcome preference and choice	*24 (77%)*
Preference for researchers to choose their own outcomes	21 (68%)
Preference for researchers to use outcomes also used in other trials	14 (45%)
Core outcome sets seen as restricting trialist choice of outcomes	10 (32%)
Knowledge about core outcome sets	*19 (61%)*
Poor knowledge about the existence of core outcome sets	19 (61%)
Poor knowledge about how to use core outcomes	6 (19%)
Measurement issues	*19 (61%)*
Patient burden	11 (36%)
Challenges identifying how to measure outcomes	9 (29%)
Costs associated with measuring the core outcomes	5 (16%)
Poor quality and design of core outcome measures[a]	2 (6%)
Challenges associated with measurement of some outcomes in an ongoing trial[a]	1 (3%)
Time spent for assessing the complete core set during trial visit[a]	1 (3%)
Applicability and relevance of core outcome sets	*16 (52%)*
Scope of existing core outcome sets	13 (42%)
Lack of applicability of core outcome sets in different geographical regions/resource settings	5 (16%)
Outcomes not specific enough for topic of the study[a]	1 (3%)
Finding and identifying core outcome sets	*10 (32%)*
Difficulties identifying appropriate core outcome sets for trials	9 (29%)
Availability of core outcome sets[a]	1 (3%)
Other	*13 (42%)*
Difficulties persuading trialists/authors/industry to use core outcome sets	12 (39%)
Competing risk of death affecting interpretability of non-mortality-based outcomes in critical care[a]	1 (3%)
Political affiliations with older outcomes[a]	1 (3%)
None	*1 (3%)*
Facilitators for core outcome set use in trials	*N* (%)
Awareness and knowledge about core outcome sets	28 (90%)
Clear understanding of what core outcome sets are	28 (90%)
Trialists are aware of the key trial outcomes[a]	1 (3%)
Positive perceptions of core outcome sets	26 (84%)
Perceived importance of core outcome sets by trialists/authors/industry	24 (77%)
Perception that core outcome set outcomes will be more appropriate for trials due to stakeholder input	16 (52%)
Recommendations for core outcome set use	24 (77%)
Recommendations by funders to use core outcome sets	22 (71%)
Recommendations by professional bodies to use core outcome sets	21 (68%)
Requirement by journal editors[a]	1 (3%)
Identification of core outcomes	23 (74%)
That core outcome sets help identify outcomes for use in trials (even if the full core outcome set is not used)	17 (55%)
How easy it is to identify a relevant core outcome set	16 (52%)
Supports for core outcome set use	16 (52%)
Availability of core outcome set guidelines and resources	16 (52%)
Measurement issues	9 (29%)
Ease of identifying relevant outcome measurement instruments for a trial	9 (29%)
Other	2 (6%)
No charges to use core outcome sets[a]	1 (3%)
Outcomes that may not have a lot of scientific value have the potential to be translated and integrated into policy and programs[a]	1 (3%)
None	0

Note. All percentages given are calculated for the full cohort of trialists completing the survey ($n = 31$)
[a] Participant self-reported barriers and facilitators in response to open-ended questions

for increased training and awareness of COS and related resources [3,20–22].

Preferences for trialists to use their own outcomes and those from previous trials were further barriers, which have been documented previously [13,15]. Such preferences may be linked to issues of perceived importance by trialists/authors/industry, which was reported as a perceived facilitator for COS use in this study. Recommendations from funders and/or professional bodies to use COS were also identified as important perceived facilitators, as noted in a previous examination of COS use in funding applications [13]. It is conceivable that endorsement from journals may similarly impact COS use. This could be done by journals in the same field working together to promote COS use, as has been done by the CoRe Outcomes in Women's and Newborn health (CROWN) initiative. Journals publishing trial protocols and registered reports are also well placed to endorse use of COS in trials or, at a minimum, require explanations for not using existing COS [23].

Limitations to the current study include a low response rate to the survey (33%), which may contribute to non-response bias. The criterion that COS available at the time of trial commencement *could* have been used in the trial may incorrectly assume that such COS *were* available to the trialists at the time of trial design. Examination of trial and COS outcome overlap did not include outcomes reported in result sections or supplementary files only, which may underestimate potential overlap. Strengths of the current study include an *a priori* published protocol [17] involving comprehensive methods to identify and examine published trials and COS, as well as elicit attitudes and experiences from clinical trialists.

In conclusion, COS use in trials in major general medical journals is low. There is a need for greater awareness of the importance of COS use. There is also a need for development and/or adaptation of COS for important clinical areas to support this COS use, as relevant COS were identified for only one-third of published trials. To address these issues, COS developers should ensure representative involvement of their research community in COS development and engage in COS dissemination to general and specialized audiences. Endorsement from journals to use and report COS in trials, or to explain and justify not using COS, may help to increase COS use in trials. These efforts will likely improve standardization of stakeholder-relevant outcomes, improve evidence syntheses, minimize research waste, and improve patient care.

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Authors contributions

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.10.012.

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