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ORIGINAL RESEARCH

Inclusion of harm outcomes in core outcome sets requires careful consideration

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Abstract

Objectives: The objective of this study was to determine the proportion of all published core outcome set (COS) studies that include an adverse event or harm outcome, to determine the proportion of individual vs pooled harms, and to investigate characteristics that influence their inclusion.

Methods: We examined the extent to which a sample of 100 published COS studies (from January 2021 to January 2023) include both pooled and individual harms in the final COS. One investigator extracted the information from the COS studies, which was cross-checked against previous COS investigational research, and where possible verified with COS authors or a pharmacologist. Using Qualtrics™, we conducted a personalized online survey of developers of the 100 COS to ask them about the importance, their experiences, and methodological approaches for dealing with harms within their COS development studies.

Results: One hundred COS were identified from 91 separate COS studies, the majority of which considered most of the minimum standards for development. Two-thirds (65%) of the COS included at least 1 harm outcome. In total, 1104 core outcomes were identified across the 100 COS, of which 184 (17%) were harm outcomes (154 individual vs 56 pooled). Individual harms were more likely to be included in a final COS if they were developed for single treatment interventions (50%) compared to those being developed for multitreatment modalities (39%). Some COS developers adopted outcome frameworks as part of their COS development process to facilitate the inclusion of harm outcomes in their final COS. A third (33%) of respondents felt that harm outcomes should be included in all COS but over half (56%) thought this would be dependent on some aspect of the scope of the COS and improved methodology and awareness of how to deal with harm outcomes in the COS development process.

Conclusion: Harm outcomes are already included in many COS either as individual or pooled harms. It is evident that there are some challenges with regards to both the methodology and necessity to include harms within a COS (pooled or individual. COS developers should carefully consider the need to include important harms outcomes in relation to the scope of the COS that they are developing.

Keywords: Adverse events; Core outcome set; Harm outcomes; Interventions; Survey; Harm reporting

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Plain language summary

COS's are a minimum group of outcomes that is agreed to be measured and reported for any trial for a particular health condition. The production of a COS involves a process that requires different stakeholders, including patients, clinicians, and researchers to reach a consensus on what is important. Unfavorable events like an adverse event resulting from a treatment may be missed in this process. This study aims to look at whether there has been a change in the inclusion of these harms within COS, what type of harms were reported, and whether their developers had a way of including harms in their work. Our methods involve looking at 100 recent COS and approaching the developers of these 100 COS using a survey, to ask them about their approach to handling harm outcomes. Two-thirds of these COS included at least 1 harm and while a third of the developers who responded felt harms should be included in the COS, over half thought it would depend on other aspects of the disease. We conclude that including harms should be considered in the COS development process but may not always be needed in the final set.

1. Introduction

In clinical practice, choosing appropriate medical interventions should be a shared process by key stakeholders (including patients) based on best evidence and consideration of individual values. This often involves balancing of benefits and harms associated with the intervention. Such decisions may be affected by outcome reporting bias for both benefits [1] and harms [2] as well as other reporting deficiencies in primary research [3].

Core outcome sets (COS's) represent an agreed-upon standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care [4]. In recent years, COS are being developed for different areas of research outside clinical trials and for routine care [5]. COS aim not only to mitigate the challenges of outcome reporting but increase the usefulness of research evidence and facilitate evidence synthesis (eg, meta-analysis) across studies [6]. Consequently, there is no obvious reason why COS should not be used when choosing outcomes in systematic reviews. This is a good practice measure that is strongly recommended in the latest edition of the Cochrane Handbook for Systematic Reviews [7,8].

There are now several hundred published COS that have each been defined by their scope, for example by: healthcare condition, population, intervention type and/or context of use (research and/or routine practice). These are freely accessible and searchable through the Core Outcome Measures in Effectiveness Trials (COMET) database (https://comet-initiative.org/Studies). As well as facilitators, there are identifiable barriers with regards to the use of COS in systematic reviews which includes lack of awareness of the COS, difficulties with implementation and the lack of resources [9,10]. Notwithstanding these issues, which may also include the scope of the COS [11] and its contextual relevance, many COS do not include important harm or adverse event outcomes. A recently developed taxonomy for classifying outcomes and applying this to COS studies revealed that only about a third (105/299) of COS included an 'adverse event' domain [12]. These would be required for reviewers to maximize the gains obtained through COS but also to undertake the necessary trade-off between the benefits and harms of interventions. A limitation of this taxonomy is that it is not intended to include any specifically named adverse events, which may be particularly important to patients when there is a well-established adverse event profile for a given intervention. An example includes anastomotic leakage following upper gastrointestinal surgery which can lead to major morbidity and even death.

To assist with the COS development process, guidance exists [13] on the minimum standard for developing COS (Core Outcome Set-STAndards for Development [COS-STAD]) but there has been little attention on how harms or adverse events should be included and or categorized within a COS.

2. Objectives

This study has 3 objectives:

I. To examine the extent to which individual or pooled harm outcomes are currently included in recently published COS development studies.
II.To understand the characteristics of these COS that include harm outcomes specifically in relation to key items set out by the minimum standards for COS development.
III. To understand how COS developers consider harm outcomes within the COS development process.

Together these objectives will explore this field with the future aim of making recommendations for including harms selection in COS.

3. Methods

This study was registered with the COMET Initiative (https://comet-initiative.org/Studies/Details/1764) and the

What is new?

Key findings

- 100 COS published studies were identified between January 2021 to January 2023.
- We found two thirds of these COS contained at least one adverse event or harm outcome.
- Survey of COS developers and authors from this sample showed 30% of respondents felt harm outcomes should be included in a final COS.
- Only 11% of survey respondents felt harm outcomes should not be included in a COS.
- The majority of COS developer-authors felt that inclusion of harm outcomes in the final COS is dependent on the scope of each COS.

What this adds to what is known?

- The proportion of COS with a reported harm outcome has now increased from 35% as reported in 2018, to 65%.
- There is no clear consensus for COS developers on handling harm outcomes in the development process.

What is the implication and what should change now?

- Further work is needed to clarify the selection process of harm outcomes in COS development.

methodological review part of the study was registered with International prospective register of systematic reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=373162).

3.1. Identification of COS studies

The COMET database is a searchable repository of COS which is kept up-to-date through annual systematic reviews, SCOPUS alerts and from notifications from COS developers. A search for COS development studies used in this methodological review was conducted on the COMET database (accessed on February 2, 2023). Eligibility was restricted to all published COS from 2021 onwards as a) this would provide the most recent studies which are expected to have better adherence to COS-STAD standards and b) would yield a potentially manageable number of identified studies as this review was aimed to look at only 100 studies. This sample size decision was a pragmatic choice, with the aim to look at a practical number of COS studies that we could assess within the available timeframe. All COS studies were eligible irrespective of area of health care or method of COS development provided they reported on a COS. If more than 100 eligible COS were identified we planned to take a random sample; conversely, if we obtained less than 100 COS we planned to widen the search back past 2021.

3.2. Data extraction

In step 1, for each eligible study, the recommended core set of outcomes were extracted by a single reviewer (JT). Extractions were checked by a member of the COMET team (SD) who had previously independently extracted data on core outcomes from a similar sample, as part of addressing a different research question. Thirty-five of the 100 COS studies used in this study overlapped and were therefore checked by both JT and SD.

In step 2, the extracted outcomes from each COS were classified by a single reviewer (JT) into either a benefit or harm outcome using any additional information in the COS development manuscript to assist with the classification. A harm outcome is defined here as an unfavorable occurrence caused by the intervention or drug [14]. Harm outcomes were additionally classified into pooled harms or individual harms. A pooled harm is a harm outcome that does not specify the exact adverse event, for example, ‘‘any adverse events’’; whereas an individual harm would be specific, for example, ‘‘anastomotic leak’’.

In the final step, 1 reviewer (JT) assessed each COS study against the COS-STAD criteria of development. The method for this assessment followed the approach used to assess cancer COS, where a total of 12 criteria represented 11 minimum standards [15]. The guidance on how to compare a published COS to the standards is presented in this previous assessment. Each criteria was assessed as ‘Yes’ (meeting the standard), ‘No’ (not meeting the standard) or ‘Unsure’ (it was unclear whether the criteria had been met). Where possible, verbatim text from the COS publication was extracted to justify whether each criteria had been taken into consideration. For the classification of benefit/harm outcomes and for the COS-STAD assessments, 10% of the COS studies were checked by a second reviewer (JJK/BA) and discrepancies were resolved through further discussion.

3.3. Survey of corresponding authors of COS development studies

The corresponding authors of the COS development studies included in the cohort were invited to take part in a short survey about their COS development study. The survey was administered using Qualtrics™ software, September 2023 version. Copyright © 2020 (https://www.qualtrics.com). This was open for responses between September 1, 2023, and November 20, 2023. The survey questions are reported in Appendix 1. The key aims of the survey were to confirm our previous data extractions and to ask COS developers about their views on the importance of including at

Table 1. COS-STAD minimum standard assessments (100 COS from 91 studies)

Domain	Standard number	Standard	Standard met *n* (%)	Standard unclear *n* (%)	Standard not met *n* (%)
Scope specification	1	The research or practice setting in which the COS is to be applied	91 (100)	0	0
	2	The health condition covered by the COS	91 (100)	0	0
	3	The population covered by the COS	91 (100)	0	0
	4	The intervention covered by the COS	91 (100)	0	0
Stakeholders involved	5	Those who will use the COS in research	89 (98)	0	2 (2)
	6	Health-care professionals with experience of patients with the condition	91 (100)	0	0
	7	Patients with the condition or their representatives	82 (90)	0	9 (10)
Consensus process	8	The initial list of outcomes considered both health-care professionals' and patients' views	80 (88)	1 (1)	10 (11)
	9a	A scoring process was described a priori	86 (95)	1 (1)	4 (5)
	9b	A consensus definition was described a priori	84 (92)	1 (1)	6 (7)
	10	Criteria for including/dropping/adding outcomes were described a priori	82 (90)	4 (4)	5 (5)
	11	Care was taken to avoid ambiguity of language used in the list of outcomes	67 (74)	14 (15)	10 (11)

COS, core outcome set; COS-STAD, core outcome set-STAndards for development.

least 1 harm outcome in a COS. We asked them if and how harms outcomes were considered during the consensus processes, whether they deployed any specific methodology to ensure a harm outcome was included in the final COS, and how influential patient or carer participants were in this decision on a scale of 0 (not influential) to 10 (most influential). In the event of a nonresponse, an expert in adverse effects methodology (YL) verified harm outcome classifications within the COS studies.

3.4. Data analysis

For each COS, the number (and percentage) of harm outcomes included within each COS was presented, taking into account the nature of the type of harm outcome (pooled or individual), and where possible the intervention item as part of the scope of the COS. Survey responses were presented descriptively and an inductive analysis was used to extract and categorize into common themes.

3.5. Ethics

In accordance with The University of Manchester's policies, formal ethics review was not necessary for this study (reference 2023-18064-30800) on the basis that personal information was collected that was readily available in the public domain, sensitive and confidential material was not discussed and vulnerable groups were not targeted in the survey that was administered.

4. Results

Based on a search of the COMET database on February 2, 2023, a total of 100 COS were screened and identified from 91 studies. Studies that reported on more than 1 COS either reported on different conditions as part of the same field of research or the same condition but for a different population, intervention or stage of disease. The concordance of agreement in classification of harms vs favorable outcome, between COS developer and researcher (JT) was 91% (600/659) outcomes. Given that agreement was high, we concluded that it would be sufficient for a single reviewer (JT) to assess outcome specification for the remainder of the COS studies where there was no COS developer response, provided a second reviewer (YL) checked the classification where there was uncertainty.

An overview of the minimum standards assessments is provided in Table 1. The standard of development across the 91 studies was deemed to be very good with 70% (64/91) of the studies meeting all 12 criteria representing the 11 minimum standards (range 6 to 12 criteria). All 91 COS studies met the 4 minimum standards for scope and 89% (81/91) studies met all standards for stakeholder involvement (ie, included those who will use the COS in research, health-care professionals and patients or their representatives). Seventy-one percent of the studies (65/91) met all 4 standards for the consensus process (Table 1).

With regards to the research or practice setting in which the COS was to be used, 54% (49/91) of studies stated that the intended used of the COS was for research (eg, clinical trials),

Table 2. Summary of the scope of the core outcome set studies included

Scope of COS	*n* (%)
Intended use of COS (*n* = 91)	
Research	49 (54)
Routine practice	22 (24)
Research and routine practice	20 (22)
Population characteristics (*n* = 92[a])	
All adults (men and women)	52 (57)
Adults (women)	7 (8)
Adults (men)	1 (1)
Adults and children	10 (11)
Older adults (65+)	4 (4)
Children	15 (16)
Young children (<2 y)	3 (3)
Intervention (*n* = 94[b,c])	
Any intervention	43 (46)
Single treatment modality	
Management of care/process	10 (11)
Drug treatments	9 (10)
Procedure	5 (5)
Surgery	5 (5)
Rehabilitation/physical activity	3 (3)
Device	2 (2)
Alternative/traditional Chinese medicine	4 (4)
Two treatment modality	
Surgery + other (e.g., postoperative management)	4 (4)
Drug + other (e.g., diet or physical activity)	4 (4)
Behavioral/psychological	2 (2)
Surveillance/education	2 (2)
Device/procedure	1 (1)

COS, core outcome set.

[a] One COS study reported separate outcomes for women and infants (pregestational diabetes).

[b] One COS study reported separate outcomes for drug and procedural treatments (sickle cell).

[c] One COS study reported separate outcomes for three different treatment modalities, surgical, nonsurgical and regenerative treatment (periodontitis.

24% (22/91) for use in routine practice and 22% (20/91) for use in clinical research and routine clinical practice (Table 2). Fifty-seven percent (52/91) of the COS studies were developed for all adults only and 47% (43/91) were developed for any type of interventions, while 42% (38/91) were developed for a single-treatment modality (Table 2). Across all 100 COS included in the 91 COS studies, a total of 1104 core outcomes were identified with a median of 9 outcomes per individual COS (IQR 6–14; min 2, max 55).

4.1. Inclusion of harm outcomes within COS studies

Sixty-five percent of the COS included at least 1 harm outcome (65/100) within the specified COS. Of the 1104 core outcomes, 81% (894/1104) were considered to be favorable outcomes, 17% (184/1104) harms and 2% (26/1104) were specified as mortality/survival. Forty-three percent (80/184) of the harm outcomes were surgical intervention-related as opposed to mixed interventions or an investigational medical product.

In the 65 COS reporting at least 1 harm outcome, the median percentage of core outcomes that were harms was 20% (range 5%–100%) (Fig). In 2 COS [16,17], all the core outcomes were considered to be harms as would be expected for studies focusing on unfavorable events. Thirty percent (56/184) of the harm outcomes were specified as a pooled harm (e.g., 'any' adverse event or all adverse events) while the remaining (128/184) were individual harms (e.g., infection or a treatment process error such as injury). Individual harms were more likely to be specified in COS that were developed specifically for single treatment interventions (50%; 19/38), than COS that were developed for more than 1 treatment modality or any intervention (39%; 22/56).

4.2. Survey of COS developers

Fifty-six COS developers replied to the survey relating to 65 separate COS within the study sample, hence we had COS developer input for 65% of the COS studies within our sample. From the survey, 17 (out of 56) COS developers reported that they had taken specific steps to support the promotion of including of at least 1 harm outcome in the final COS. For 6 of these an underpinning framework was used (e.g., OMERACT filter [18]) to ensure that a core harm domain was defined as part of the preplanned methodology, which facilitated the inclusion of harms in the final COS. For a further 2, including harm was implicit because the aim was to develop a core harm set (2 cases mentioned above). In further 9 COS's, developers were satisfied that all relevant harms outcome were included in the consensus process (as part of generating the 'long list', COS-STAD item 8) but relied only on the consensus criteria to determine whether these made it into the final core set. In 3 of these, a harm was included in the final COS because of a strong steer by the steering group/consensus meeting members.

Moving forward, 30% (17/56) of COS developers thought that harms should be included in COS, while 11% (6/56) said that they should not be included while 54% (30/56) said that it would be dependent on the circumstances. Of the 25 suggestions made, 18 of these inferred that the inclusion of a harm would depend on some aspect of the scope of the COS (9 cited the

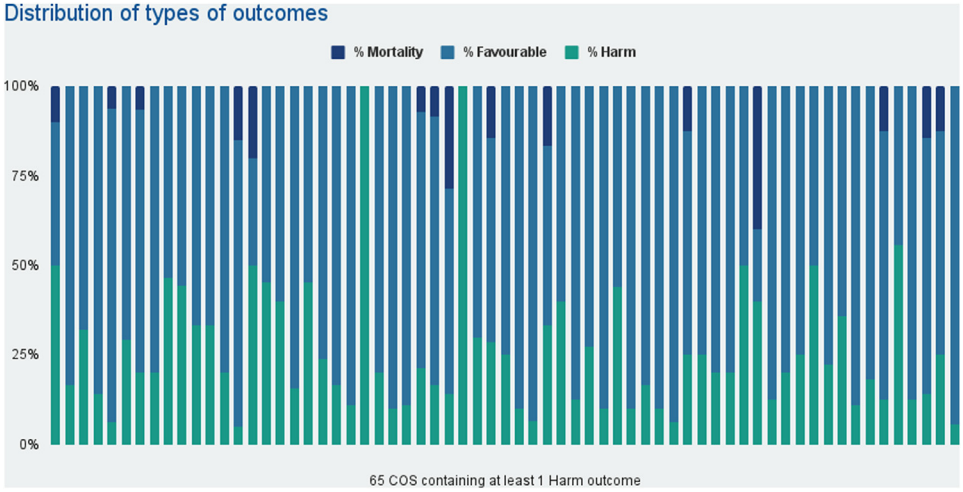

Figure. Distribution of types of outcomes.

condition; 7 cited the intervention; 1 cited the intended purpose of use; and 1 population). Other suggestions demonstrated more uncertainty about inclusion because of the current lack of robust methodology to develop COS that ensures harms are included (4 mentions) while some developers wondered if harms within COS were needed at all, as there is an expectation (in research) that all harms should always be reported irrespective of inclusion within a COS (3 mentions).

On the 11-point Likert scale of how influential the patient's or carer participant's opinions was on the decision of including an adverse event outcome, the median score was 8; range 0−10.

5. Discussion

Two-thirds of the most recent COS development studies reported here included a harm outcome. This was considerably more than the third of COS studies that found an 'adverse event' domain in the earlier taxonomy work [12]. This increase can be anticipated given individual harms were considered in this study which found that under a third of the harm outcomes in this study were 'pooled' items.

In terms of the COS development process, most studies appeared to rely on use of the consensus criteria to 'vote in' these harm outcomes. The survey data showed that sometimes harms were included into the final COS at a late stage in the consensus. Very few developers adopted alternative preplanned methodology to ensure a harm was included when appropriate [19−21]. Outcomes frameworks such as the OMERACT filter [18] was the only methodological approach used to facilitate harm inclusion if they were appropriate to include. Within this framework, developers can place harms (or adverse events) into core areas, and where appropriate core domains of harm can be optionally specified for consideration in the final COS.

With respect to the appropriateness for harm inclusion in a COS, the majority of developers that responded believed that this would partly depend on the context or scope of the COS. For many clinical conditions, harms may be appropriate because they can seriously affect a patient's quality of life [22], treatment adherence [23] and the financial cost to patients and health systems [24]. This is especially important in invasive interventions like surgery [25]. However, a detailed assessment of specific harms associated with interventions for serious health conditions may be considered relatively lower priority by researchers and practitioners because they are conceptualized as being rare events [14].

In trials research, harm reporting is already mandated by governing bodies such as Health Research Authority and Food and Drug Administration. An absence of harms reported may misrepresent the intervention as a safe option, regardless of the efficacy or benefit of the intervention [26]. For this reason this opens the debate as to whether there is a need to include harms in COS at all, whether 'adverse events' as a broad (pooled) term is acceptable as a core outcome, or whether specific adverse events are important enough to include as separate core outcomes. Despite the ideology that all harms should be reported in research, there is a plethora of evidence that suggest harm reporting is poor [27,28] and maybe prone to outcome reporting bias [2]. The existence of a COS has been described as a potential solution to address the problem of outcome reporting bias [4]. [7] also commented on some of these difficulties in harms reporting. One suggestion of theirs was to consider producing a core harm outcome set alongside a COS to capture clinically important adverse events, even if rare. Notably, 2 COS's in our study were developed specifically as adverse event−only outcome sets [16,29].

The COS development process currently does not necessitate the inclusion of a harm outcome. The COS-STAD

[13] guidelines with regards to the consensus process only ensure outcomes are considered by relevant stakeholders and not any particular type of outcome. What is included in the final COS is rightly driven by the development process itself. While it might be resource intensive to produce a core harm outcome set on its own, an adaptation within the existing COS development process might be a more feasible solution. Important harms should either directly be included in each COS or at least be collated as part of the process within COS studies even if they do not make the final COS. This is coherent with the long-standing suggestion that outcomes should not be restricted to just those within a COS [4].

Although there was an increase in the inclusion of individual harms when a COS was developed for single intervention types, our survey respondents suggested that harm inclusion may be related to different aspects of COS scope. The inclusion of harms within a COS may be more complex than other outcomes. For example, important harms could be related to additional aspects of the condition such as disease progression or severity of harm.

The main strength of our study was that it was preregistered with PROSPERO and for many of the COS studies included, COS extraction was double checked by a COMET representative (SD) and in the majority of cases by the COS developers themselves, the latter also applying to the delineation of benefit and harm outcomes. This study is set to be the first to challenge the inclusion, or absence of, harm outcomes within COS development. One limitation of our study is the use of a survey, which does not allow for more in-depth exploration of the responses. To meet our study's objective (iii), some of the free text answers were not sufficient. The main researcher (JT) had multiple teleconferences, phone calls and emails with respondents to follow-up on responses that lacked detail or clarity. A semistructured interview could have provided this adequately; however, performing, transcribing and analyzing semistructured interviews for 91 authors was not pragmatically feasible within the scope of this study. Finally, our study did not specifically identify any composite outcomes within the included COS which may represent both benefit and harm outcome, but the successful uptake of some COS can be dependent on the use of composite outcomes [30].

6. Conclusion

Many harm outcomes are included in COS and this seems to be increasingly common. Challenges in the selection of harms whether pooled or individual remain and this needs further work. The decision on which harms to include is inherently complex and likely related to elements of the scope of the COS. Harm outcomes should be routinely considered in the COS development process though for some COS it is may not be a necessity that they are included in the final COS.

CRediT authorship contribution statement

Joel Tay: Writing − original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Catherine Robinson:** Methodology. **Jane Blazeby:** Writing − review & editing. **Yoon Loke:** Writing − review & editing, Methodology. **Aoife Lowery:** Writing − review & editing. **Bilal Alkhaffaf:** Writing − review & editing, Supervision, Methodology, Conceptualization. **Jamie J. Kirkham:** Writing − review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

J.J.K and J.B. are members of the Core Outcome Measures in Effectiveness Trials Initiative. There are no competing interests for any other author.

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Supplementary data

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