STUDY PROTOCOL

Representation of published core outcome sets for research in regulatory guidance: protocol [version 1; peer review: 1 approved with reservations]

Susanna Dodd, Rebecca Fish, Sarah Gorst, Deborah Hall, Pamela Jacobsen, Jamie Kirkham, Barry Main, Karen Matvienko-Sikar, Ian J. Saldanha, Dominic Trépel, Paula R. Williamson

1MRC/NIHR Trials Methodology Research Partnership, Department of Health Data Science, University of Liverpool (a member of Liverpool Health Partners), Liverpool, UK
2Division of Cancer Sciences, University of Manchester, Manchester, UK
3Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK
4Hearing Sciences, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, UK
5School of Social Sciences, Heriot-Watt University Malaysia, Putrajaya, Malaysia
6Department of Psychology, University of Bath, Bath, UK
7Centre for Biostatistics, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK
8University of Bristol Medical School, Centre for Surgical Research, Bristol, UK
9School of Public Health, University College Cork, Cork, Ireland
10Center for Evidence Synthesis in Health; Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island, USA
11Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland
12School of Medicine, Trinity College Dublin, Dublin, Ireland
13University California, San Francisco, California, USA

Abstract

Background: The COMET Initiative promotes the development and use of ‘core outcome sets’ (COS), agreed standardised sets of outcomes that should be measured and reported in all studies in a particular clinical condition. COS are determined by consensus amongst key stakeholders, including health professionals, policymakers and patients, ensuring that the priorities and expertise of these representatives inform the choice of the most important outcomes to measure for a given condition. There is increased recognition of the need to integrate COS across the healthcare system and with existing regulatory apparatus, to ensure that outcomes being recorded are those of key relevance to important stakeholders. The aim of this study is to assess the degree of concordance between outcomes recommended in COS for research and in guidance provided by two key regulators: US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

involvement and covering drug or device interventions will be compared against relevant regulatory guidelines, matched by condition. Guidance documents which match in scope (relating to intervention and population) to a COS for research will be scrutinised to identify all suggested outcomes for comparison against the core outcomes in the corresponding COS.

**Discussion:** This study will identify variation between outcomes suggested in EMA and FDA regulatory guidance relative to outcomes included in published COS for research, thus demonstrating the degree of representation of COS in regulatory guidance and vice versa. If the findings of this study reveal a lack of concordance between COS and regulatory guidance overall or for particular disease areas, we will invite feedback from FDA and EMA and will seek to highlight where findings support the recommendations towards using well-developed COS or will make recommendations to COS developers on outcomes of importance to these key regulators.

**Keywords**
core outcome sets, regulatory guidance
Introduction

It is important to measure patient health outcomes in order to inform healthcare decisions made by patients, healthcare professionals and funders. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative supports those involved in the development of “core outcome sets” (COS), which are defined as the minimum set of outcomes that should be measured and reported in all studies in a particular clinical condition. COMET provides and maintains an online publicly available searchable database of completed and ongoing COS development projects which is continually being updated by way of annual systematic reviews. COS may be developed for research and/or clinical practice, and are determined by consensus amongst key stakeholders, including health professionals, policymakers and patients, ensuring that the priorities and expertise of these representatives inform the choice of the most important outcomes to measure for a given condition. There is increased recognition by trial funders and healthcare organisations of the importance of considering COS. The Core Outcome Set-STAAndards for Development (COS-STAD) minimum standards provides 11 criteria on which to judge the quality of COS, relating to three aspects of the COS development process: scope (health condition, population and intervention), stakeholder involvement (including patients, health professionals and researchers) and consensus process (including the initial potential outcomes lists, scoring and consensus decisions, and unambiguous wording of outcomes).

Healthcare regulators play an important role in quality improvement, and frameworks adopted by certain organisations rely on evidence on outcomes to inform decision-making. Specifically, as an example, to support improvement in healthcare services in the UK, bodies such as the Healthcare Quality Improvement Partnership (HQIP) or UK National Institute for Health and Care Excellence (NICE), are recognising the relevance of considering COS for consistent measurements to inform their guidance. In 2018, NICE guidance on methods to determine relevant guideline outcomes was updated to indicate that COS should be used, if suitable based on quality and validity. The HQIP tool describing key features of national clinical audits and registries states that the rationale for quality improvement objectives should take into account relevant evidence from the COMET database.

A number of research funding agencies (particularly those commissioning the use of pragmatic randomised control trial to inform policy and regulation) are increasingly recommending that applicants should consider using a COS if one exists. For example, the international SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) reporting guidelines endorse consulting the COMET database to identify relevant COS, and in the UK, as an example, National Institute for Health Research Health Technology Assessment (NIHR HTA) programme refers applicants to the COMET database, suggesting that they include established core outcomes “unless there is good reason to do otherwise”. The authors believe that uniformity in recommendations from NIHR and other public funders regarding use of COS would promote greater consistency in outcome collection globally. This benefit would have additional impact if the consistency in such recommendations extended to those from commercial sponsors. The NIHR is a unique health funding agency as Technology Assessment Review teams are funded to provide NICE with independent research to inform their guidance committees. Whilst the relationship between funding research and regulating health varies internationally, regulators such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are influential in commissioning of research to help inform their decisions and it is important to assess the degree of concordance between patient outcomes suggested in FDA and EMA guidance and core outcomes included within COS for research, matched by condition.

The US FDA publishes official Guidance Documents and other regulatory guidance, covering topics such as biologics, drugs, medical devices and food, as well as general guidance on study design and outcomes, such as their guidance on the conduct of randomised trials during the coronavirus disease 2019 (COVID-19) pandemic or on Patient-Reported Outcome Measures. These guidance documents describe the FDA’s current opinion on regulatory issues but are not legally binding (unlike FDA regulations, which are federal laws). Similarly, the EMA publishes scientific guidelines prepared in consultation with regulatory authorities in the European Union Member States to inform marketing authorisation applications for human medicines, with full justification required for any deviations from these guidelines. This study will compare the outcomes suggested in these guidance documents against core outcomes included within COS, matched by condition, in order to progress this field by furthering our understanding of the similarities and the differences between COS and guidelines.

Methods

Study design

This study will involve searching for, and extracting outcomes of importance mentioned in, EMA and FDA guidelines which match in population and intervention scope to COS for research identified from the COMET database. The cohort of COS for research included in this study will be those published during 2015–2019 which involved patients in the consensus process and whose scope covers drugs and/or devices, thus ensuring a relatively high quality selection of COS of relevance to regulatory guidelines, for comparison against relevant EMA/FDA guidelines matched by condition and intervention.

Search strategy

The COMET database contains 106 COS for research published between 2015 and 2019 which involved patients in the consensus process. Selection of only those COS published in the last five years which involved patients will increase the number of COS-STAD (Core Outcome Set-STAAndards for Development) standards met. The scope of the COS meeting these criteria will be assessed to ensure that they cover drugs or devices,
and if not, they will be excluded from the cohort. For each COS for research, we will search the FDA15 and EMA16 websites to identify guidance covering the relevant disease/condition, using the key clinical terms as search terms. If necessary, we will refine these searches using the Google site-specific search facility e.g. searching for “diabetes site: fda.gov” or “diabetes site: ema.europa.eu” when searching for guidelines relating to diabetes on the FDA or EMA websites respectively. We will engage with COS developers if clinical input is required for guidance on appropriate search terms (e.g. to determine synonymous clinical terms to those used to describe the disease/condition under investigation in the COS) or if there is any ambiguity regarding whether identified guidance documents match the scope of the COS (in terms of the disease/condition or interventions). Searches for guidelines matching each COS will be carried out independently by two researchers.

Selection process
We will initially identify regulatory guidance/COS pairs where the scope is an exact match but will also consider situations where one of the pair may be more general than the other, based on an assessment of the descriptions of the population (i.e. clinical condition/disease) and intervention in the COS publications and regulatory guideline documents, using a previously-developed framework21 (see Figure 1). For example, if the COS was relevant for patients with chronic pain and FDA/EMA guideline was relevant for any type of pain (i.e. COS population is narrower), and both the COS and FDA/EMA guideline were specified as being relevant to medicinal projects alone (i.e. an exact match in intervention scope), this COS/guideline pair would be assigned scope matrix classification ‘b’. If the COS population and FDA/EMA guideline population matched exactly, but the COS intervention scope covered any intervention compared to the FDA/EMA guideline which related only to drug interventions, (i.e. COS intervention is broader), this pair would be assigned the scope matrix classification ‘g’. Pairs which focused on different interventions or different populations will not be considered to be a match (i.e. only matches corresponding to types a-c. e-g, i-k in Figure 1 will be eligible for inclusion). Two reviewers will independently apply this scope matching algorithm to each pair of FDA/EMA guideline and corresponding potentially relevant COS. Discrepancies will be resolved through discussion.

Eligibility
- COS will be eligible if they meet the following inclusion criteria:
  o COS for research (including those intended for both research and practice)
  o COS published between 2015 and 2019
  o COS involved patients in the consensus process
  o COS intervention scope covers drug or device interventions.

- EMA/FDA regulatory guidance documents will be eligible for comparison against relevant COS for research if they meet the following inclusion criteria:
  o Guideline scope (in terms of intervention and population i.e. clinical condition/ disease) matches at least generally with that of the corresponding COS for research (i.e. matches of type a-c. e-g, i-k in Figure 1), i.e.
    - COS intervention scope is narrower, broader or an exact match compared to EMA/FDA guideline intervention scope, and
    - COS population (clinical condition/ disease) scope is narrower, broader or an exact match compared to EMA/FDA guideline population scope.

![Figure 1](https://via.placeholder.com/150)

**Figure 1.** Scope matching algorithm determined according to the descriptions of the population and intervention within the FDA/EMA guideline versus the corresponding COS. COS=core outcome sets; FDA=US Food and Drug Administration; EMA=European Medicines Agency.
Data extraction

Data on the year of publication, disease name, specific condition and outcomes included in the eligible published COS for research will be exported from the COMET database and COS database into an Excel spreadsheet. Once FDA and EMA guidance documents are identified which match in scope to a COS for research, the guidance documents will be scrutinised in order to identify all suggested outcomes (i.e. those outcomes which the guidelines state should/could/may/might be considered) relating to the specific COS population and intervention. Any additional caveats included in the guidelines about each of the recommended outcomes (e.g. relating to the age category or severity) will be recorded. If specific measurement tools (e.g. quality of life questionnaires) are recommended, the reviewer will search for and extract the individual items within these measurement tools, in order to assess whether these individual items correspond to any outcomes recommended by the corresponding COS/guidelines. Verbatim guidance document text regarding the suggested outcome measures will be recorded in tabular form for each COS. The matching between the scope of the COS and regulatory guidance will be classified as exact or general (e.g. COS is narrower/broader) in relation to both the population with the condition and the interventions (as per Figure 1), with input from clinical members of the research team and/or the COS developers, if necessary. Data extraction will be carried out by all researchers for the initial three COS/guidance pairs to ensure consistency of approach; subsequent data extraction will be carried out independently by two researchers. Disagreements will be resolved by discussion with SD/PW if necessary. Mapping between core outcomes and outcomes suggested in guidelines will be checked by the lead author (SD).

Analysis

The mapping of the verbatim extracted text from the EMA/FDA guidance to each of the core outcomes will be coded as specific (i.e. direct correspondence between the wording of the core outcome references in the guidance compared to the wording in COS) or general (i.e. only general alignment between the wording of text in the guidance relative to the wording in the COS), and this mapping will be summarised using a table as demonstrated for the type 2 diabetes SCORE-IT COS in Table 1. Again, we will contact COS developers if clinical input is required regarding general or specific correspondence.

Table 1. Tabulated results for SCORE-IT COS (T2D case study).\(^{22}\)

<table>
<thead>
<tr>
<th>SCORE-IT COS</th>
<th>Guidance</th>
<th>SCORE-IT core outcome not explicitly mentioned but covered by the following general terms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMA</td>
<td>FDA</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from a diabetes related cause such as heart disease</td>
<td>(✓)(^{a})</td>
<td>(✓) (✓)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>(✓)(^{b})</td>
<td>(✓)(^{b})</td>
</tr>
<tr>
<td>Gangrene or amputation of the leg, foot or toe</td>
<td>(✓)(^{a})</td>
<td>(✓)</td>
</tr>
<tr>
<td>Hyperglycaemic emergencies(^{1})</td>
<td>(✓)(^{a})</td>
<td>(✓)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>(✓)(^{a})</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>✓(^{4})</td>
<td>(✓)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>✓</td>
<td>(✓)</td>
</tr>
<tr>
<td>Hospital admissions due to diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects of treatment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Global quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>(✓)(^{b})</td>
<td>(✓)(^{b})</td>
</tr>
<tr>
<td>Visual deterioration or blindness</td>
<td>(✓)(^{a})</td>
<td>(✓)</td>
</tr>
<tr>
<td>Glycaemic control</td>
<td>✓(^{4})</td>
<td>✓</td>
</tr>
<tr>
<td>Neuropathy(^{2})</td>
<td>✓</td>
<td>(✓)</td>
</tr>
<tr>
<td>Kidney function</td>
<td>✓</td>
<td>(✓)</td>
</tr>
<tr>
<td>Activities of daily living(^{3})</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>✓(^{4})</td>
<td></td>
</tr>
</tbody>
</table>

1 Including diabetic ketoacidosis and hyperosmolar hyperglycaemic state  
2 Damage to the nerves caused by high glucose. This can lead to tingling and pain or numbness in the feet or legs. It can also affect bowel control, stomach emptying and sexual function.  
3 Including those related to personal care; household tasks or community-based tasks.  
4 Included as core efficacy or safety outcome
between core outcomes and those suggested in the guidance. We will use a tick to demonstrate specific correspondence between the wording of the core outcome references in the guidelines compared to the wording in COS, whereas a tick in brackets will be used to indicate general alignment (with further detail provided in a footnote) between the wording of suggested outcomes in the guidelines relative to the wording in the COS. For each COS, we will record the number (and percentage) of COS outcomes which were covered in the guidance (separately for FDA and EMA) in general or specific terms (separately) and either general/specific terms. The distribution of these percentages will be summarised across guidance documents as a whole, split by FDA and EMA, using descriptive statistics and graphical presentation, overall and split by disease category. We will also present results according to the breakdown of matching between scope of intervention and population between the COS and guidelines, as shown in the matrix in Figure 1. Note that only results for highlighted cells a-c, e-g, i-k will be presented (i.e. those corresponding to at least a general match in both intervention and population between the COS and guidelines).

In addition, by way of symmetry we will present the results above which instead compare how the core outcomes relate to those suggested in EMA and FDA guidelines, in order to identify the agreement of COS with outcomes suggested in corresponding guidelines; i.e. we will present two additional sets of tables/results, the first with outcomes suggested in the EMA guidelines, and the second with outcomes suggested in the FDA guidelines, as the index list of outcomes.

Dissemination

The findings of this study will be disseminated through publication in an open access peer-reviewed journal and presentation at both national and international conferences. Contact will be made with FDA and EMA colleagues and feedback on our findings requested.

Study status

Eligible COS have been identified and searches for matching EMA/FDA guidelines for each eligible COS (with searching and scope matrix classification being carried out independently by two reviewers for each eligible COS) is currently underway. Pilot data extraction for three COS/guideline pairs has been undertaken by all reviewers.

Discussion

This study will identify any misalignment between outcomes suggested by EMA and FDA regulatory guidance relative to those included in published COS for research, thus demonstrating the degree of representation of core outcomes, which have been agreed by consensus by key stakeholders, within regulatory guidance, and vice versa. A lack of concordance between COS and regulatory guidance may highlight the opportunity for such guidelines to be better informed by COS and vice versa, and we will use the evidence obtained from this study to engage the relevant regulatory bodies in discussions accordingly.

Data availability

No data are associated with this article.

References

Thank you for letting us review this interesting study. We think the research question is well chosen and will give interesting insights and results of the use and applicability of COS. We only have some minor comments which we hope will be helpful in improving the study further.

1. In the last sentence of the Discussion part in the abstract, the authors state that they will seek feedback from FDA and EMA “if there is a lack of concordance between COS and regulatory guidance overall or for particular disease areas.” We think feedback from the regulatory authorities would be interesting regardless of what the results are.

2. As the COMET database in our understanding includes studies from different countries, we suggest that an example from another country than the UK as well, is included in the introduction to give a broader perspective. As it reads now, there seems to be only the UK or “globally”.

3. Regarding methods, it is stated that the studies should have been published between 2015-2019. Why is 2020 not included (as we are in 2021 now). Please explain why this is: because of COVID-19, nothing was published or any other reason.

4. We currently think there is a lack of discussion on the potential limitations of the study. For example, limitations regarding relevance and context. It would be interesting to see whether a COS -set produced in a high-income country compared to a low-income country differ, and also, if one or the other has influenced EMA or FDA more. We understand that there could be difficulties in drawing conclusions out of this type of information, however it is important to discuss the potential importance of this implication which in the long run may mean that the production of COS will have impact on research outcomes of thus more
importance to high-income countries. (Patients or other stakeholders may look upon the prioritization of outcomes differently depending on contextual factors).

5. There is also a lack of discussion on the quality of the included COS. In the section on methods, we think the authors should add a paragraph on how they will assess quality of the included COS. This should be discussed regarding both the selection of participants, how the actual prioritization process is done as well as numbers of the outcomes included in the core outcome set. (Core outcome sets that include large number of outcomes will likely have more of a concordance with regulatory guidance than those with fewer outcomes. It is our opinion that a core set by definition should include less than 10 outcomes, but when it doesn't this needs to be addressed.

6. It would be interesting if the authors note whether the included published core outcome sets had searched for FDA or EMA documentation regarding important outcomes before they started their study.

7. Finally, we assume the authors will discuss how researchers should relate to core outcome sets that do not include all the requested outcomes requested by regulators. That will be an interesting discussion to read. Looking forward to see this study published!

**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Yes

**Are the datasets clearly presented in a useable and accessible format?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health Technology Assessment (HTA)

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.