Representation of core outcomes in regulatory guidance from the FDA and EMA

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TITLE
Representation of core outcomes in regulatory guidance from the FDA and EMA

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Tables: 4
Figures: 2

APPENDICES

Appendix Figures: 1

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ABSTRACT

Objectives
We conducted an analysis to compare outcomes included within published core outcome sets (COS) against the outcomes recommended in corresponding European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) guidance documents, matched by health condition.

Study Design
We included a sample of COS related to drugs, devices, and gene therapy that involved patients in the consensus process and were published between January 1, 2015, and December 31, 2019.

Outcomes
We assessed the extent of matches between outcomes included within COS and those recommended in corresponding EMA and FDA guidance documents. When outcomes were matched, we considered matches to be general (i.e., non-specific) or specific (i.e., exact). For general matches, we assessed whether the COS or guidance document outcome was narrower.

Results
We found relevant guidance documents for 38/98 eligible COS (39%). Among outcomes in COS, medians of 70% [interquartile range (IQR) 48% to 86%] and 52% [IQR 33% to 76%] were matches with outcomes in EMA and FDA documents, respectively. Medians of 46% [IQR 27% to 68%] and 26% [IQR 18% to 46%] were specific matches with outcomes in EMA and FDA documents, respectively. When outcomes were generally matched, the COS outcome was more frequently narrower than the regulatory outcome (83% and 75% for EMA and FDA, respectively).

Conclusions
Greater adoption of, and reference to, COS in regulatory guidance documents can encourage clinical trialists, especially those in industry, to measure and report consistent and agreed outcomes and improve the quality of guidance. Given the overlap between outcomes in COS and regulatory guidance, and given that most COS now involve patients in the consensus process, COS could serve as a useful resource for regulators when recommending outcomes for studies evaluating regulated products. We encourage COS developers to appraise recommended outcomes in salient regulatory documents when planning a COS.
KEY MESSAGES

What is already known about this subject?

Core outcome sets (COS) are agreed standardized sets of outcomes within specific clinical topic areas. Clinical trialists are highly influenced by regulators of drug and device products.

What are the new findings?

We assessed the extent of matches between outcomes included within COS and those recommended in corresponding FDA and EMA guidance documents. Among outcomes in COS, medians of 70% [interquartile range (IQR) 48% to 86%] and 52% [IQR 33% to 76%] were matches with outcomes in EMA and FDA documents, respectively.

How might these results change the focus of research or clinical practice?

Given the overlap between outcomes in COS and regulatory guidance, and given that most COS now involve patients in the consensus process, COS could serve as a useful resource for regulators when recommending outcomes for studies evaluating regulated products. We encourage COS developers to appraise recommended outcomes in salient regulatory documents when planning a COS.
INTRODUCTION

What are Core Outcome Sets?

Core outcome sets (COS) are agreed standardized sets of outcomes within specific clinical topic areas.¹ COS are developed to inform either research or clinical practice and are generally determined by an initial systematic review (to identify all potential outcomes), followed by a process to prioritize the most important outcomes based on consensus among health professionals, researchers, policymakers, and patients or their representatives.² The Core Outcome Measures in Effectiveness Trials (COMET) Initiative brings together individuals and groups working on developing and applying COS and improving COS development methodology.³,⁴ COMET maintains a free, publicly available, searchable database of completed and ongoing COS development projects.³

The two main reasons why COS are developed are because they help ensure that (1) the priorities and expertise of key stakeholders inform the recommended set of outcomes to measure in clinical trials for a given health condition, and (2) the results of those trials, having reported at least the core outcomes in common, can be incorporated into systematic reviews and meta-analyses to inform regulatory and healthcare guidance and decision making.⁵⁻¹¹

Increasing Recognition of the Importance of COS

COS use is increasingly recommended by a broad set of stakeholders in the evidence ecosystem, including trial funders and those who use the results of trials (e.g., policymakers).¹² Several trial funders, such as the U.K. National Institute for Health Research (NIHR), the U.S.
Patient-Centered Outcomes Research Institute (PCORI), the Irish Health Research Board (HRB), and the Netherlands Organisation for Health Research and Development (ZonMw), recommend that applicants for trial funding should consider using a COS if one exists.\textsuperscript{13} For example, the NIHR refers applicants to the COMET database, suggesting that established core outcomes be included “unless there is good reason to do otherwise.”\textsuperscript{14} The SPIRIT \textit{reporting guidelines} for clinical trial protocols recommends that trial authors consult the COMET database to identify relevant COS when choosing outcomes for the trial.\textsuperscript{15,16} Organizations that rely on evidence to support improvement in healthcare services (e.g., the Healthcare Quality Improvement Partnership [HQIP]\textsuperscript{17}) and to inform decision-making (e.g., the U.K. National Institute for Health and Care Excellence [NICE]\textsuperscript{18}) are also recognizing the relevance of COS in their work. The HQIP tool describing key features of national clinical audits and registries states that the rationale for quality improvement objectives should consider relevant outcomes from the COMET database.\textsuperscript{17} 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.\textsuperscript{18}

Notwithstanding the increase in endorsements of COS by various bodies, trialists are also highly influenced by regulators of drug and device products. Although regulatory guidelines are not legally binding documents, they are an important source of guidance for trialists. Two of the world’s prominent healthcare regulators are the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The EMA publishes scientific guidelines to inform marketing authorization applications for human medicines.\textsuperscript{19} Similarly, the FDA publishes official Guidance Documents and other documents covering various classes of regulated
products, such as biologics, drugs, medical devices, and food. The FDA also publishes general guidance on study design and outcomes, such as guidance on the conduct of randomized trials during the COVID-19 pandemic and on the use of patient-reported outcome measures. Both EMA and FDA guidance are highly influential on what research is commissioned, particularly where evidence gaps are a source of uncertainty for existing guidance.

COS are developed using methods that incorporate patient and clinician (and other stakeholder) preferences for outcomes. Therefore, if suggested outcomes in regulatory guidance documents align with COS, this would bring these salient outcomes to the attention of investigators as they design their clinical trials. As a first step, we need a better understanding of the similarities and differences between outcomes included in COS and outcomes recommended by regulatory bodies. To our knowledge, a systematic assessment of the degree of concordance between outcomes included within COS and outcomes recommended in FDA and EMA guidance documents, matched by health condition, has not been conducted.

Objective
We compared core outcomes included within COS against the outcomes recommended in EMA and FDA guidance documents, matched by health condition.

METHODS
We published the protocol for this study prospectively.
Selection of COS

We examined all COS for research (including those intended for both research and practice) that involved patients in the consensus process and were published between January 1, 2015, and December 31, 2019. Selection of only those COS published in the last 5 years (at the time of beginning our study) that involved patients likely increased the number of standards of the Core Outcome Set-Standards for Development (COS-STAD\textsuperscript{2}) that are met by this sample of COS. To maximize relevance to regulatory guidance, we restricted the sample to those COS relating to any intervention or specifically to drug, device, or gene therapy interventions; we excluded COS relating exclusively to surgical interventions because procedures are not subject to EMA or FDA regulatory oversight.

Identification of Matching Regulatory Guidance Documents

For each eligible COS, we identified EMA/FDA guidance documents that address similar health conditions, published up to April 2021. Because we are not aware of a readily searchable electronic database for guidance documents, we searched websites of the EMA\textsuperscript{19} and FDA,\textsuperscript{20} using the key clinical terms and synonyms as search terms. We refined these searches using Google’s site-specific search capability. For example, if searching for guidance documents relating to diabetes, we searched for “diabetes site: fda.gov” on the FDA website and for “diabetes site: ema.europa.eu” on the EMA website. We considered addenda to guidance documents as separate guidance documents because they usually refer to different target populations and/or interventions from the original documents. A COS could be matched to more than one guidance document, and vice-versa. For all COS, two investigators (from among
IJS, SD, RF, SLG, DH, PJ, JJK, and DT, each of whom is experienced in COS development and/or methodology) independently ran searches for guidance documents and resolved disagreements in search results through discussion, consulting SD and PW as needed.

Assessing Overlap in Scope Between COS and Matched Guidance Documents

We considered the scope of a given COS as the reference and any given regulatory guidance document to match if they were at least generally matched in terms of both clinical condition/disease and intervention. We used a previously developed framework by Saldanha et al. to assess the overlap (Figure 1A). We considered COS and regulatory documents to be matched only in scenarios represented by cells A-C, E-G, or I-K (i.e., those corresponding to at least a general match in both intervention and population between the COS and guidance document). Table 1 provides examples of these scenarios.
### Table 1: Examples of overlap in scope between COS and matched guidance documents

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Population</th>
<th>Intervention</th>
<th>Example COS title</th>
<th>Example guidance document title</th>
<th>Regulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>COS is narrower</td>
<td>COS is narrower</td>
<td>How to evaluate the clinical outcome of joint-preserving treatment for osteonecrosis of the femoral head: Development of a core outcome set</td>
<td>Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis</td>
<td>EMA</td>
</tr>
<tr>
<td>B</td>
<td>COS is narrower</td>
<td>Exact match</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>C</td>
<td>COS is narrower</td>
<td>COS is broader</td>
<td>Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 diabetes (SCORE-IT): a patient and healthcare professional consensus on a core outcome set for type 2 diabetes</td>
<td>Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus</td>
<td>EMA</td>
</tr>
<tr>
<td>E</td>
<td>Exact match</td>
<td>COS is narrower</td>
<td>Achieving consensus on minimum data items (including core outcome domains) for a longitudinal observational cohort study in rheumatoid arthritis</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>F</td>
<td>Exact match</td>
<td>Exact match</td>
<td>Achieving consensus on minimum data items (including core outcome domains) for a longitudinal observational cohort study in rheumatoid arthritis</td>
<td>Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis</td>
<td>FDA</td>
</tr>
<tr>
<td>G</td>
<td>Exact match</td>
<td>COS is broader</td>
<td>Toward Establishing Core Outcome Domains for Trials in Kidney Transplantation: Report of the Standardized Outcomes in Nephrology-Kidney Transplantation Consensus Workshops</td>
<td>Delayed Graft Function in Kidney Transplantation: Developing Drugs for Prevention</td>
<td>FDA</td>
</tr>
<tr>
<td>I</td>
<td>COS is broader</td>
<td>COS is narrower</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>J</td>
<td>COS is broader</td>
<td>Exact match</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>K</td>
<td>COS is broader</td>
<td>COS is broader</td>
<td>Chronic rhinosinusitis outcome Measures (CHROME) – developing a core outcome set for trials of interventions in chronic rhinosinusitis</td>
<td>Nonallergic Rhinitis: Developing drug products for treatment</td>
<td>FDA</td>
</tr>
</tbody>
</table>

Abbreviations: COS = core outcome set, EMA = European Medicines Agency, FDA = Food and Drug Administration.

**Extracting Information from COS**

For each COS, we used an existing database of previously extracted information regarding recommended core outcomes. This database contains all published COS and is compiled using data extracted for an annually updated systematic review of published COS. We also
reviewed the article(s) describing each COS (also obtained from the COMET Database) to confirm the list of core outcomes. In the one instance where an article recommended additional outcomes but specified that these were not part of the COS (adverse events in a COS for hemophilia\textsuperscript{28}), we included those outcomes when comparing the COS to the regulatory document because those outcomes were recommended. We also assessed whether the COS referred to the corresponding regulatory document.

*Extracting Information from Guidance Documents*

To facilitate standardized data extraction across the team, all investigators participated in an initial pilot exercise using two pairs of COS and regulatory documents. After that, for the remaining data extraction, two investigators (from among IJS, SD, RF, SLG, DH, PJ, JJK, and DT) independently extracted all outcomes from each pair of COS and regulatory guidance document. We extracted outcomes regardless of the outcome’s location in the document or the outcome’s status as primary, secondary, or other. Disagreements between pairs of extractors were resolved by discussion among the pairs and, when needed, with SD.

*Matching of Outcomes Between COS and Relevant Guidance Documents*

We focused on the outcome domains (“what,” e.g., pain). We did not examine whether the “how” of an outcome (e.g., one pain measurement instrument versus another) matched. We considered matching of outcomes separately for each pair of COS and guidance document.
Consistent with previous work,\textsuperscript{9,29} we considered an outcome in a COS and an outcome in a guidance document to be matched if they were generally or specifically related. Outcome pairs were thus matched \textit{generally} if one document specified a broad outcome (e.g., “disease activity”), while the other was more explicit (e.g., “joint damage”) or \textit{specifically} if both documents specified the same explicit outcome (e.g., “overall survival” and “all-cause mortality”).

Measurement instruments (e.g., multi-component quality of life questionnaires) recommended in guidance documents deserve special mention. If the outcome instrument recommended in a guidance document overlapped with a core outcome in a COS, we considered the outcomes as \textit{generally} matched if the guidance outcome included an overall summary measure that covered more domains (e.g., health-related quality of life) than simply the COS outcome (e.g., physical functioning) or \textit{specifically} matched if the instrument covered only the COS outcome.

For all generally matched pairs of outcomes, we also assessed which of the two outcomes was broader.

\textit{Statistical Analyses}

We calculated descriptive statistics (percentages and medians with interquartile ranges [IQRs]) for COS and relevant guidance documents. We calculated the median percentages of outcomes in COS that were specific matches, general matches, and non-matches with outcomes in
relevant guidance documents overall as well as separately for EMA and FDA. We constructed scatter plots and used kernel (nonparametric) smoothing to depict potential relationships between percentage matching (i.e., percentage of outcomes in the COS that were matched to outcomes in the guidance documents) and the number of outcomes in the COS. For the kernel smoothing, we used the rule of thumb (ROT) method to calculate window sizes. We conducted all analyses using Stata Version 16 (College Station, Texas, USA). We estimated the median (and IQR) of the proportion of outcomes that overlapped between the COS and guidance documents.

RESULTS

Included COS

Based on a search of the COMET database, a total of 108 COS for research, with patients included in the consensus process, were published between January 1, 2015, and December 31, 2019 (Figure 2). We excluded 10 COS for relating to specific interventions other than drugs, devices, or gene therapy.

Among the remaining 98 COS, we identified at least one regulatory guidance document for 38 COS (39%). Table 2 summarizes these 38 COS. Just under a third of these 38 COS (32%) were published in 2017. The most frequent topic areas were neurology (18%), cancer (13%), gastroenterology (13%), and pain (11%). Most COS (82%) were not developed for a specific type of intervention (i.e., they were developed for any intervention). The 38 COS included a median
of 8 outcomes (IQR 6 to 11). None of the COS referred to the corresponding regulatory document(s).

Table 2: Characteristics of the 38 core outcome sets included in this analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Core Outcome Sets (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td><strong>Year of publication</strong></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>6</td>
</tr>
<tr>
<td>2016</td>
<td>3</td>
</tr>
<tr>
<td>2017</td>
<td>12</td>
</tr>
<tr>
<td>2018</td>
<td>9</td>
</tr>
<tr>
<td>2019</td>
<td>8</td>
</tr>
<tr>
<td><strong>Topic area</strong></td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>7</td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>5</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Allergy or infections</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td><strong>Type of intervention targeted</strong></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>31</td>
</tr>
<tr>
<td>Drugs</td>
<td>4</td>
</tr>
<tr>
<td>Devices/surgeries</td>
<td>2</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Number of outcomes in core outcome set</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>(6, 11)</td>
</tr>
<tr>
<td>Range</td>
<td>(2, 38)</td>
</tr>
<tr>
<td>Mean</td>
<td>10.0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*COS and EMA Guidance Documents – Overlap in Timing and Scope*

We found 29 matching EMA guidance documents for 35 COS (Figure 2). These EMA guidance documents were published between 2005 and 2021. There were 44 pairs of COS-EMA
documents. The COS was published before the EMA document in 15/44 pairs (34%), in the same year in 5/44 pairs (11%), and after the EMA document in 24/44 pairs (55%).

**Figure 1B** depicts these 44 pairs. The COS is very likely to be relevant for 21/44 pairs (48%) and may be relevant for 23/44 pairs (52%). The most frequent was scenario ‘C’ (i.e., the COS population was narrower than the EMA guidance document, but the COS described a broader intervention or set of interventions than the EMA guidance document) (21/44 pairs; 48%). Both the population and the intervention in the COS and EMA guidance were exact in scope (i.e., scenario ‘F’) in only one pair (2.3%).

**COS and FDA Guidance Documents – Overlap in Timing and Scope**

We found 21 matching FDA guidance documents for 24 COS (Figure 1). These FDA guidance documents were published between 1981 and 2020. There were 30 pairs of COS-FDA documents. The COS was published before the FDA document in 12/30 pairs (40%), in the same year in 4/30 pairs (13%), and after the FDA document in 14/30 pairs (47%).

**Figure 1C** depicts these 30 pairs. The COS is very likely to be relevant for 22 pairs (73%) and may be relevant for eight pairs (27%). For one in five pairs (20%), both the population and the intervention were exact in scope (i.e., scenario ‘F’).

**COS and EMA Guidance Documents – Overlap in Outcomes**

For the 44 pairs of COS and EMA guidance documents, a median of 70% of outcomes in the COS
(IQR 48% to 86%) were specific or general matches to outcomes in corresponding guidance documents (Table 2). A median of 46% (27% to 68%) were specific matches. Where there was a general match in outcomes, the EMA outcome was broader in 83% and the COS outcome was broader in 17%.

The scatter plot in Appendix Figure 1A suggests a generally inverse relationship between the number of outcomes in the COS and the percentage match between the outcomes in the COS and the EMA guidance document. This was true for all matches (blue smoothed curve) as well as for specific matches in particular (green smoothed curve).

COS and FDA Guidance Documents – Overlap in Outcomes

For the 30 pairs of COS and FDA guidance documents, a median of 52% of outcomes in the COS (IQR 33% to 77%) were specific or general matches to outcomes in corresponding guidance documents (Table 3). A median of 26% (IQR 18% to 46%) were specific matches. Where there was a general match, the COS outcome was narrower in 75% and broader in 25%.

<table>
<thead>
<tr>
<th>Pairs</th>
<th>Specific Matches</th>
<th>General Matches</th>
<th>Specific or General Matches</th>
</tr>
</thead>
<tbody>
<tr>
<td>COS and FDA (44 pairs)</td>
<td>46% [27%, 68%]</td>
<td>13% [0%, 27%]</td>
<td>70% [48%, 86%]</td>
</tr>
<tr>
<td>COS and FDA (30 pairs)</td>
<td>26% [18%, 46%]</td>
<td>11% [0%, 37%]</td>
<td>52% [33%, 77%]</td>
</tr>
</tbody>
</table>

Abbreviations: COS = core outcome set, EMA = European Medicines Agency, FDA = U.S. Food and Drug Administration, IQR = interquartile range.
The scatter plot in Appendix Figure 1B suggests a generally inverse relationship between the number of outcomes in the COS and the percentage match between the outcomes in the COS and the FDA guidance document. This was true for all matches (blue smoothed curve) as well as for specific matches in particular (green smoothed curve).

**Examples of Matching**

Table 4 provides examples of specific matches, general matches, and non-matches between pairs of outcomes in EMA/FDA guidelines and outcomes recommended in corresponding COS. For generally matched outcomes, the table also includes our assessment of whether the COS outcome was narrower, broader, or neither.
Table 4: Examples of specific matches, general matches, and non-matches between outcomes in EMA/FDA guidance documents and corresponding relevant core outcome sets

<table>
<thead>
<tr>
<th>Clinical Area</th>
<th>Outcome in EMA/FDA Guideline</th>
<th>Outcome In COS</th>
<th>Type of Match</th>
<th>Comparative Assessment of Breadth of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>Pain intensity</td>
<td>Pain intensity</td>
<td>Specific</td>
<td>-</td>
</tr>
<tr>
<td>Back pain</td>
<td>Quality of life</td>
<td>Health related quality of life</td>
<td>Specific</td>
<td>-</td>
</tr>
<tr>
<td>Neuro-disability</td>
<td>Sleep disturbance</td>
<td>Sleep</td>
<td>Specific</td>
<td>-</td>
</tr>
<tr>
<td>Neuro-disability</td>
<td>Behavioural reactions</td>
<td>Behaviour</td>
<td>Specific</td>
<td>-</td>
</tr>
<tr>
<td>Back pain</td>
<td>Emotional functioning</td>
<td>Depression</td>
<td>General</td>
<td>Outcome in COS is narrower.</td>
</tr>
<tr>
<td>Neuro-disability</td>
<td>Activities of daily living</td>
<td>Toileting</td>
<td>General</td>
<td>Outcome in COS is narrower.</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Symptomatic improvement</td>
<td>Angina</td>
<td>General</td>
<td>Outcome in COS is narrower.</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>Quality of life</td>
<td>Diabetes-related quality of life</td>
<td>General</td>
<td>Outcome in COS is narrower.</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Overall survival</td>
<td>Death from prostate cancer</td>
<td>General</td>
<td>Outcome in COS is narrower.</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Nocturnal hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>General</td>
<td>Outcome in COS is broader.</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Time to need of radical therapy</td>
<td>Treatment failure</td>
<td>General</td>
<td>Outcome in COS is broader.</td>
</tr>
<tr>
<td>Rolandic epilepsy</td>
<td>Coordination</td>
<td>Gross motor function</td>
<td>General</td>
<td>Outcome in COS is broader.</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Relapse</td>
<td>Employment</td>
<td>Not a match</td>
<td>-</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>Analgesic Use</td>
<td>Utility</td>
<td>Not a match</td>
<td>-</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Body weight</td>
<td>Perceived level of control over diabetes</td>
<td>Not a match</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: COS = core outcome set, EMA = European Medicines Agency, FDA = Food and Drug Administration.

DISCUSSION

Summary of Findings

In this analysis, just under 40% of recent (2015 to 2019) COS were on topics with relevant EMA or FDA regulatory guidance documents. A median of 70% of outcomes in COS were specific or general matches to outcomes in EMA guidance documents, and almost half (46%) were specific...
(i.e., exact) matches. Corresponding proportions for pairs of COS and FDA guidance documents were approximately half (52%) and quarter (26%), respectively. When outcomes were generally matched, the COS outcome was more frequently narrower than the guidance outcome.

**Numbers of Outcomes**

The current analysis finds a generally inverse relationship between the number of outcomes in COS and the percentage of those outcomes that were either specific or general matches to outcomes recommended in corresponding guidance documents, both EMA and FDA. This finding contradicts the lack of a relationship that we previously demonstrated between the number of outcomes in COS and the percentage of overlap with outcomes in systematic reviews on the same topic.⁹ We believe that because of the purpose that regulatory guidance documents (examined in the current analysis) serve, they may focus on the most important outcomes of interest for the research question. COS with fewer outcomes are also more likely reflect developers’ efforts to prioritize the most important outcomes. This might explain why COS with fewer outcomes in the current analysis had a greater percentage overlap with outcomes in regulatory guidance. It is possible that COS developers recommending a greater number of outcomes may have adopted a more inclusive view of what a COS should constitute. Another potential reason for the difference between our current findings and our prior findings (similar analysis comparing COS and systematic reviews⁹) may relate to the different purposes and intended audiences of regulatory guidance documents and systematic reviews.
Regulatory Document Purposes

When regulatory bodies, such as the EMA and the FDA, issue guidance on study design (including outcome choice), the guidance is intended to guide the design, analysis, and reporting of studies that evaluate regulated products. But, regulatory bodies approve claims made in product labels, not the products themselves. So, regulators are often flexible about which outcomes are included in trials because the general focus of regulators is on determining whether the evidence presented supports the claim about clinical benefit that the manufacturer wants included on the product label.

In the context of regulatory document purposes, surrogate (i.e., intermediate) outcomes are another issue worth discussing. Because trials may not be powered for, and/or may not have long enough follow-up for, longer-term clinical outcomes, it is plausible that regulatory guidance for such studies is more accepting of surrogate outcomes than are developers of corresponding COS (who generally first prioritize outcomes based on importance rather than feasibility). Kalf and colleagues have suggested that although practices vary across regulators, regulators generally accept surrogate outcomes. However, the issue of surrogate outcomes in recent FDA guidance on emerging disease-modifying therapies for dementia has been a source of concern and merits careful consideration and clearer methodological guidance. In the current analysis, we did not evaluate the extent to which surrogate outcomes were
recommended and how that might vary comparing regulatory documents and COS. This is a potential area for future research.

*Implications for COS Developers*

At the outset, COS developers should consider the eventual uptake of the COS being developed. COS developers should appraise related regulatory guidance documents in the topic area when planning a COS; none of the included COS reported doing this. We also agree with Aiyegbusi and colleagues that (1) regulators may be relevant stakeholders in outcomes recommended in COS (especially for COS related to drugs, devices, and gene therapy); (2) greater collaboration between COS developers and regulators is warranted; and (3) regulators should participate in COS development. Participation of regulators may be important because it may enable their preferences (along with those of others) to be considered in the COS development process. However, there may be bureaucratic restrictions that preclude their participation in COS. How best to engage regulators in COS development and adoption process remains to be explored. Nevertheless, greater adoption of COS in regulatory guidance documents has the potential to push clinical trialists, especially those funded by industry, to measure and report outcomes from COS.

*Implications for Regulators*

The processes of outcome selection for inclusion in regulatory guidance documents generally includes an initial selection by agency staff, followed by input obtained through meetings with clinical experts, patients, and various stakeholders, and engagement with the public. Although
this input may sometimes include alerting regulators about relevant COS, the extent to which COS are being consistently considered in this process is unclear.

Regulators are, however, increasingly recognizing the importance of engaging patients in the regulatory process.\textsuperscript{36,37} As part of its Patient-Focused Drug Development (PFDD) efforts, the FDA has developed a set of methodological guidance documents to help various stakeholders “collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making.”\textsuperscript{38} All the COS examined in the current analysis (and almost 40% of COS developed by 2019\textsuperscript{7} and over 90% of ongoing COS [unpublished work]) have involved patients in the development process. Regulators should capitalize on this engagement of patients (and various other stakeholders), which is a great strength of the COS development process.

Regulators should also be reassured that the overlap in outcomes between COS and existing corresponding regulatory documents is good. The current analysis finds that as many as 70% of outcomes in COS were matched to outcomes in corresponding EMA guidance documents and 52% to outcomes in corresponding FDA guidance documents. Thus, COS could serve as a useful resource for regulators when recommending outcomes for studies evaluating the regulated products.

The majority of COS in this analysis were published in the same year or after the matched guidance document (66% of COS-EMA pairs and 60% of COS-FDA pairs). Nevertheless, our
results support the two main actions that have been suggested for regulators. First, when drafting a new or updated guidance document, regulators should review the COMET database for evidence about relevant high-quality COS for the scope of the guidance and consider those outcomes when developing regulatory guidance. Second, regulators should engage with the COS development process to help identify barriers and facilitators early on.

**Challenges in Conducting this Analysis**

We encountered some challenges during this analysis that are worth discussing. First, we included COS for research, recognizing that these are not only intended for randomized trials but also for non-randomized studies. However, this choice was reasonable because regulatory guidelines issued by the EMA or FDA target both randomized trials and non-randomized studies. Second, there were some instances that required us to make particularly careful decisions regarding the match in scope between the COS and the guidance document. For example, one eligible COS addressed interventions for patients on hemodialysis. We found an EMA guidance document addressing primary prevention of chronic kidney disease in at-risk groups or secondary prevention (i.e., early interventions to prevent worsening of kidney function). We did not consider the COS and the guidance document to be a match because hemodialysis is an example of a treatment for established and advanced chronic kidney disease (i.e., hemodialysis is a form of tertiary prevention). Third, when extracting outcomes from guidance documents, it was not always clear whether the document was truly recommending a particular outcome. This required judgement in discerning potentially ambiguous language, such as that the outcome “should,” “could,” “might,” or “may” be considered, or that the
outcome “is important.” Some of this ambiguity in language may have arisen because guidance from regulatory bodies regarding outcome choices in studies of regulated products generally is non-binding.

Limitations
The current analysis has some limitations. First, the COS we analyzed were restricted to those with patient involvement in consensus generation, which is what is recommended by COS-STAD.² However, these COS may not be representative of all COS. Among all COS published by 2020, those that involved patients included a somewhat larger number of outcomes (median 8, IQR 5 to 12) than those that did not involve patients (median 6, IQR 3 to 8) (COMET, personal communication). Therefore, given the inverse relationship between the number of outcomes in a COS and the percent overlap between COS and regulatory outcomes (documented in this paper), it is perhaps likely that the overlap may have been higher had we looked at a sample of COS without patient involvement. The COS in the current analysis represented a recent 5-year sample, and the level of adherence to COS-STAD standards (including patient involvement) has generally been improving.⁷ ²₄ ²₇ Second, although we applied our systematic search methods for guidance documents consistently, it is possible that we missed some guidance documents from the EMA or FDA. Third, for regulatory guidance documents, we restricted our search to the EMA and FDA. Although the EMA and FDA are two prominent healthcare regulatory bodies, we recognize that there are others in other regions and countries. As such, our findings should be inferred to be informed by guidance produced by the EMA and FDA.
Conclusions

In summary, we found sizeable overlap between outcomes in COS and in corresponding EMA and FDA guidance documents. We encourage COS developers to involve regulators in COS development and to consider outcomes recommended in regulatory guidance documents. We encourage regulators to engage with the COS development process (to help identify barriers and facilitators early on) and, when drafting a new or updated guidance document, to review the COMET database for relevant high-quality COS.
CONTRIBUTORSHIP STATEMENT

*Study concept and design:* Dodd and Williamson. *Acquisition of data:* Saldanha, Dodd, Fish, Gorst, Hall, Jacobsen, Kirkham, and Trepel. *Analysis:* Saldanha. *Interpretation of data:* All authors. *Drafting of the manuscript:* Saldanha. *Revising manuscript for intellectual content:* All authors. *Final approval of the completed manuscript:* All authors.

COMPETING INTERESTS

PRW and SLG are members of the Core Outcome Measures in Effectiveness Trials (COMET) Management Group.

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DATA SHARING STATEMENT

Data will be shared by the contact author upon reasonable request.

ETHICS APPROVAL AND CONSENT STATEMENT

Ethics approval and consent were not required because all data used in this analysis are based on publicly available core outcome sets and regulatory guidance documents.
REFERENCES


FIGURE TITLES AND LEGENDS

Figure 1 Title
Disposition of COS and EMA and FDA guidance documents in this analysis

Figure 1A Title
Framework for comparing scope between pairs of COS and matching guidance documents (from Saldanha et al. 20219)

Figure 1B Title
Completed framework for 44 pairs of COS and EMA regulatory guidance documents in this analysis

Figure 1C Title
Completed framework for 30 pairs of COS and FDA regulatory guidance documents in this analysis

Figure 2 Title
Disposition of COS and EMA and FDA regulatory guidance documents in this analysis

Figure 2 Legend:
Abbreviations: COMET = Core Outcome Measures for Effectiveness Trials, COS = core outcome set, EMA = European Medicines Agency, FDA = U.S. Food and Drug Administration.
A COS could be relevant to multiple regulatory guidance documents and vice-versa.

APPENDIX FIGURE TITLES AND LEGENDS

Appendix Figure 1 Title
Scatter plots of percentage match in outcomes between COS and EMA and FDA guidance documents versus number of outcomes in COS

Appendix Figure 1A Title
For EMA guidance documents

Appendix Figure 1B Title
For FDA guidance documents

Appendix Figure 1A and Figure 1B Legend
Each COS and guidance document pair has two dots, one dot for the percentage of outcomes that are either specific or general matches (blue dot) and another dot for the percentage of outcomes that are specific matches (green). The curves are generated using kernel (nonparametric) smoothing.