Selection of Core Outcome Sets (COS)

The DO→IT project aims to provide guidance to BD4BO projects and is developing a toolkit to support current and future projects in 'the identification, selection, and measurement of outcomes in real-world settings'. Agreed standardised sets of outcomes are known as 'core outcome sets' (COS). These sets of outcomes are the agreed minimum standardised set of outcomes that should be measured and reported in trials or other research on a specific condition.

This toolkit will be completed for use by the disease-specific BD4BO projects at the end of **April 2018**. The toolkit will cover existing methods for developing COS in trial settings and how these methods may differ for determining COS in real-world settings; it will also cover practical considerations like the needs of different decision-makers which should be considered.

The toolkit will have a particular focus on:

- Considering the needs of key decision-makers such as regulators and health technology assessment (HTA) bodies
- Incorporating patient perspectives
- Patient-reported outcome measures
- Opportunities for collecting outcomes in real-world settings

Until full guidance is provided in the form of a toolkit, we have created this summary to inform projects which are currently undertaking work in the standardisation of outcomes. This includes an overview of why there is a need for COS, existing initiatives in determining COS, stakeholders who may be involved in developing COS and methods used.

1. The need for COS

As all BD4BO projects are working on enablers for the transition towards an assessment based on different data sources, an important focus for all projects is in the **definition of outcomes** which should be measured to demonstrate the impact of a new medicine on health and/or wellbeing and on selecting a **core set of these outcomes**.

In most disease areas, there is a lack of consistency in the outcomes reported across trials as well as collected in registries or routine care.

- This makes it difficult when wanting to pool all the evidence to inform healthcare or policy decisions.
- The outcomes reported in the literature may also be biased, where studies reporting positive or significant results may be more likely to be published.[i]
- The outcomes collected are also not necessarily the ones that are important to practitioners and patients.

Organisations who make the later decisions about access of these medicines to patients (i.e. regulators, HTA bodies, payers) have specific evidence needs to make their decisions; consequently, it is essential to consider the perspectives of these decision-makers when determining what data should be collected and what should form part of the core outcome sets.

2. Existing initiatives in determining COS

There are a number of existing initiatives related to determining these standard sets of outcomes. The COMET initiative (COMET - Core Outcome Measures in Effectiveness Trials) is an international network of trialists, systematic reviewers, health service users, practitioners, editors, funders, policy makers, and regulators. The initiative aims to raise awareness of current problems with outcomes in clinical trials; encourage the development of COS; and provide resources to enable the development of COS. As part of the last objective, the COMET initiative have developed a database of existing studies that have developed COS which is updated annually. The database includes COS in all current disease areas under the BD4BO initiative. COMET have also recently published a handbook to 'bring together current thinking and methodological research' related to development COS. They are currently working on minimum standards for developing COS.

While the COMET initiative focuses on the development of COS, it does not extend to developing COS. There are a number of groups with experience in developing COS, many of which are captured within the COMET database.

The International Consortium for Health Outcomes Measurement (ICHOM) is a group with experience developing standard sets of outcomes for routine or real-world settings across a range of disease areas such as depression & anxiety, dementia, and prostate cancer. ICHOM focus, in particular, on developing standard sets of outcomes that matter most to patients.

Some groups focussed on developing COS in specific disease area include OMERACT for rheumatoid arthritis and IMMPACT for pain.

3. Importance of including multiple stakeholders

The relevance of different stakeholders will vary depending on the disease area but clinical experts and the public are important to all. Considering which stakeholders were included in selecting previously developed COS may be a means to identify suitable stakeholders groups to involve, although it may be worth critically assessing if some stakeholder groups were excluded. Including all stakeholders for whom the COS is relevant assures that the COS is acceptable to all.

Those who know what it's like to live with the effects of a condition and treatments are well placed to contribute on what outcomes are important. Without including patients, the COS may omit important outcomes. Resultantly the research can fail to fully show whether a treatment benefits patients or not. In developing COS, clinicians do not necessarily select

the same outcomes which are of importance to patients. Previous research has shown that COS differ depending on the stakeholders involved in their selection.[ii] [iii] [iv] Patient-relevant outcomes such as mortality, morbidity, quality of life, pain, or costs often require a longer follow-up time and/or larger patient numbers to obtain sufficient power to show a difference than is usual in clinical trials though this may be more feasible in real-world settings.

Including authorities, non-clinical experts and industry representatives may assist with ensuring the COS developed is acceptable to payers and that the research can be useful to policy makers and influence practice. It is increasingly accepted that having diverse stakeholders try to reach a consensus is the way forward for quality, collaborative influential research.[v]

Patients and their representatives can be identified via clinics, patient societies, advocacy groups and care giver support groups.

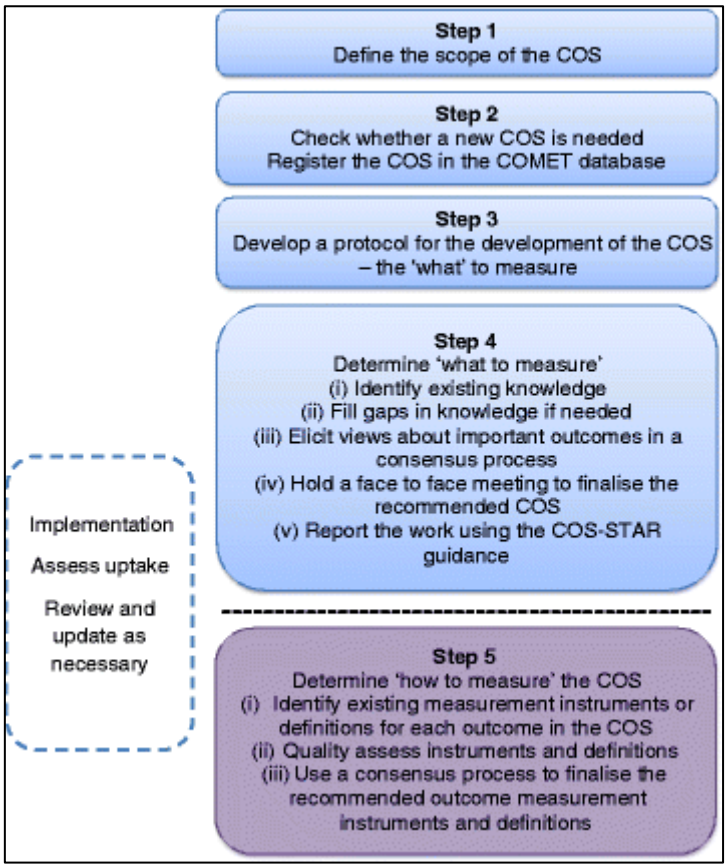
Table 1: Potential stakeholders to include in COS development

Potential stakeholders to include	Sub-category (not mutually exclusive)
Clinical experts	Clinical experts Clinical research experts Clinical trialists/members of a clinical trial network
Public representatives	Patients Patient representative organisations Carers Patient support group representatives Service users
Non-clinical research experts	Researchers Statisticians Epidemiologists Methodologists Academic research representatives
Authorities	Regulatory agency representatives HTA bodies Payers Governmental agencies Policy makers
Industry representatives	Pharmaceutical industry representatives Device manufacturers Biotechnology company representatives
Others	Ethicists Journal editors

4. Overview of COS development

The COMET Handbook provides guidance on the development, implementation, evaluation and updating of COS. The approach to COS development covered in the handbook is illustrated in Figure 1 below[vi].

Figure 1: Steps in COS development (COMET Handbook)



The table below is an example taken from an article (under review) which recommends minimum standards for COS development. These standards were developed by an international group of COS developers and users as well as methodologists, journal editors and patient representatives. The standards relate to the three aspects of COS development: defining the scope, identifying relevant stakeholders and ensuring a transparent consensus process.

Table 2: Standards in COS development

Domain	Standard number	Methodology
Scope specification	1	The research or practice setting(s) in which the COS is to be applied
	2	The health condition(s) covered by the COS
	3	The population(s) covered by the COS
	4	The intervention(s) covered by the COS
Stakeholders involved	5	Those who will use the COS in research
	6	Healthcare professionals with experience of patients with the condition
	7	Patients with the condition or their representatives
Consensus process	8	Initial list of outcomes considered both healthcare professionals' and patients' views
	9	A scoring process and consensus definition were described a priori
	10	Criteria for including/dropping/adding outcomes were described a priori
	11	Care was taken to avoid ambiguity of language used in the list of outcomes

This section gives an overview of a variety of methods which can be used in determining in 'what' to measure. Further details are in the COMET Handbook.

Table 3: Potential methods to include in COS development

Objective	Method
To identify initial outcomes for inclusion	Systematic review
	Literature review
	Search Medline / Embase / CINAHL, the Cochrane database of systematic reviews, PsycINFO
	Additional sources relevant to disease
	Suggestions from stakeholders
Review of initial outcomes list	Delphi process
	Nominal group technique
	Consensus development conference
	Qualitative interviews
	Focus groups
	Surveys
Consensus	Further rounds of Delphi
	Consensus meeting

Methodological considerations

- What sample size should be pursued (for Delphi, qualitative and surveys)?
- What response rate and level of attrition is acceptable (for Delphi, qualitative and surveys)?
- Should different methods be used for different stakeholders?
- Are the descriptions of outcomes accessible to all stakeholders? E.g. are lay and clinical explanations of outcomes needed?
- Should different types of stakeholders be brought together for consensus meetings or should be held separately?
- Should consensus meetings be face-to-face, by teleconference or online?
- How many iterations of reviewing outcomes should be undertaken?
- What constitutes a majority or 'consensus'?

5. Additional resources on methods

The steps and methods presented in Section 4 are not exhaustive, nor are any of these advocated as best practice. Selecting methods and stakeholders to develop a COS should be appropriate to the disease area and scope of the outcomes. Below are a list of useful resources to inform this process.

Gargon, E., Gurung, B., Medley, N., Altman, D.G., Blazeby, J.M., Clarke, M. and Williamson, P.R., 2014. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PloS one*, *9*(6)

Gorst, S.L., Gargon, E., Clarke, M., Blazeby, J.M., Altman, D.G. and Williamson, P.R., 2016. Choosing important health outcomes for comparative effectiveness research: an updated review and user survey. *PLoS One*, *11*(1)

Prinsen, C.A., Vohra, S., Rose, M.R., Boers, M., Tugwell, P., Clarke, M., Williamson, P.R. and Terwee, C.B., 2016. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set"–a practical guideline. *Trials*, *17*(1), p.449.

Williamson, P.R., Altman, D.G., Blazeby, J.M., Clarke, M., Devane, D., Gargon, E. and Tugwell, P., 2012. Developing core outcome sets for clinical trials: issues to consider. *Trials*, *13*(1), p.132.

Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., Clarke, M., Gargon, E., Gorst, S., Harman, N. and Kirkham, J.J., 2017. The COMET Handbook: version 1.0. *Trials*, *18*(3), p.280.

Young, B. and Bagley, H., 2016. Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates. *Research Involvement and Engagement*, *2*(1), p.25.

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[i] Dwan, K., Altman, D.G., Arnaiz, J.A., Bloom, J., Chan, A.W., Cronin, E., Decullier, E., Easterbrook, P.J., Von Elm, E., Gamble, C. and Ghersi, D., 2008. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PloS one*, *3*(8), p.e3081.

[ii] Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, De Wit M, Hazes M, Richards P, Saag K, Suarez-Almazor M. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. J Rheumatol. 2007;34(5):1174–7

[iii] Harman, N.L., Bruce, I.A., Kirkham, J.J., Tierney, S., Callery, P., O'Brien, K., Bennett, A.M., Chorbachi, R., Hall, P.N., Harding-Bell, A. and Parfect, V.H., 2015. The importance of integration of stakeholder views in core outcome set development: otitis media with effusion in children with cleft palate. *PLoS One*, *10*(6), p.e0129514

[iv] Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials. 2012;13(1):103.

[v] Williamson, P.R., Altman, D.G., Blazeby, J.M., Clarke, M., Devane, D., Gargon, E. and Tugwell, P., 2012. Developing core outcome sets for clinical trials: issues to consider. *Trials*, *13*(1), p.132.

[vi] Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., Clarke, M., Gargon, E., Gorst, S., Harman, N. and Kirkham, J.J., 2017. The COMET Handbook: version 1.0. *Trials*, *18*(3), p.280.