Big Data for
Better Outcomes

A PRACTICAL TOOLKIT

FOR THE IDENTIFICATION, SELECTION AND MEASUREMENT OF OUTCOMES INCLUDING IN REAL-WORLD SETTINGS

IMI DO→IT DELIVERABLE 2.2

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CONTRIBUTIONS

The work on this toolkit was led by the National Institute for Health and Care Excellence (NICE). Stages 2, 4, 5 and parts of the section 'Evidence for all' were drafted by the following members of the DO→IT WP2 Toolkit Working Group: London School of Economics and Political Science (LSE), the Centre for Research on Health and Social Care Management (CERGAS), Bayer, and European Multiple Sclerosis Platform (EMSP).

In addition to the above members of the Toolkit Working Group, the toolkit was reviewed by: University of Liverpool, Pfizer, Imperial College London, Bayer, Norwegian Medicines Agency (NOMA), Health iQ, Servier, and Janssen.

The authors and contributors the individual pieces of work completed to support the toolkit are noted within each appendix where the work and findings are described.

Additionally, the report was reviewed by partners in the wider BD4BO programme, University College London and the International Consortium for Health Outcomes Measurement (ICHOM) on behalf of BigData@Heart, University of Edinburgh and Roche on behalf of ROADMAP, and LeukraNet and Takeda on behalf of HARMONY.

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EXECUTIVE SUMMARY

The overall aim of the Big Data for Better Outcomes (BD4BO) programme is to facilitate the use of 'big data' in the development of a more value-based and outcomes-focused healthcare systems Europe.

One of the ways the programme is supporting this objective is through the standardisation of outcomes in different disease areas. Collecting the same outcomes across a range of sources has many advantages including enabling the pooling of outcome data across a wider population. Individual disease-specific projects are developing minimum sets of outcomes (often referred to as core outcome sets (COS)). When agreeing a COS, incorporating a wide range perspectives enables outcomes important to a number of important stakeholders to be collected.

This toolkit has been developed by the Coordination and Support Action of the BD4BO programme, DO→IT, as a practical guide for the individual disease-specific BD4BO projects to support the projects in the identification, selection and measurement of a COS in their disease area.

The toolkit proposes six main stages to develop a COS, from scoping to dissemination, with a focus on stakeholder input across all stages to ensure a wide range of perspectives are taken into account. Whilst the toolkit highlights any existing best practice to developing COS, it importantly also presents a range of methodological options which BD4BO projects can consider depending on the scope of the work and resources available. Each stage includes decision-making flowcharts, summaries of key considerations and presents case studies to highlight the key factors and considerations when developing COS. These typically reflect aspects that are of importance to BD4BO projects around the use of data from a range of sources from 'real world settings in addition to clinical trials.

INTRODUCTION

This toolkit aims to provide guidance on the identification, selection, and measurement of outcomes for current and future disease-specific projects within the Big Data for Better Outcome (BD4BO) programme across a range of settings, from those collected in the real world[1] to clinical trials (1). The toolkit includes both methodological and practical considerations about how to incorporate outcome preferences relevant to all stakeholders. It was developed by the overarching Coordination and Support Action project for the BD4BO programme, DO→IT, addressing objective 1 of work package 2 "to identify best practices for data management and the collection of outcomes".

In addition to supporting BD4BO projects, this toolkit will also be useful for organisations in Europe or internationally intending to initiate big data collection or considering the alignment of outcome selection and standardisation within a disease area. The toolkit (and appendices) may be useful for regulators, health technology assessment (HTA) agencies and payers, clinicians and trialists to better understand the differing levels of acceptability of outcomes across jurisdictions, and the reasons for these differences. It may also encourage stakeholders to further promote the standardisation of outcomes more widely.

Many of the methods related to the standardisation of outcomes are still developing and there is currently no 'gold standard' method. Generally, the initial focus tends to be on the 'what' (which outcomes should be prioritised and collected) and then the 'how' (which instruments or definitions should be used to measure these outcomes) can be addressed. The toolkit refers to a number of options for core outcome set (COS)[2] developers to choose from, and highlights any existing best practice, where available.

For the purposes of the toolkit, the definition of 'outcome' refers to clinical outcomes which are used to demonstrate the effect of a medicine on a person's health or wellbeing. Clinical outcomes should be clinically and patient-relevant, and may also be patient-reported (2,3). Other data requirements are covered in the section 'Beyond the COS'.

BIG DATA FOR BETTER OUTCOMES PROGRAMME

The overall aim of the Big Data for Better Outcomes (BD4BO) programme is to enable 'big data' to be used to develop more value-based and outcomes-focused healthcare systems in Europe (82).

The linking of big data sources comes with a number of challenges including data quality and ethical and technical questions that will result from the use of data across jurisdictions (83). The BD4BO projects each create a multi-stakeholder platform to address enablers of the use of big data across different disease areas.

A key enabler for each BD4BO project is the development/definition of minimum or standard sets of outcomes in a disease area (82). This should enable the harmonisation and combination of prospectively collected data.

http://bd4bo.eu

1. Real-world (RW) settings are those in which real-world data (RWD) is collected (see Glossary). While terminology for RWD varies, IMI GetReal have referred to RWD as "an umbrella term for data regarding the effects of health interventions…that are not collected in the context of highly-controlled RCTs…it can be either primary research data or secondary research data derived from routinely collected data…RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases" (73,74).

2. COS have been defined as "an agreed standardised set of outcomes… [that] represent the minimum that should be measured and reported in all clinical trials of a specific condition, and are also suitable for use in clinical audit or research" (18).

BIG DATA

The concept of 'big data' varies, but is generally understood to be the 'the information asset characterized by such a high volume, velocity and variety to require specific technology and analytical methods for its transformation into value' (4). In terms of healthcare, it typically refers to 'routinely or automatically collected datasets, which are electronically captured and stored' for multiple purposes (5).

This may refer to sources traditionally categorised as real-world (RW) data, including administrative databases (e.g. on hospital discharge), electronic health records, and disease registries, but can also refer to digital data collected automatically by machines (e.g. to monitor clinical status) or by patients, and wearable technology. Some data collected in the context of a typical clinical trial can be classified as big data; for example, digital technology may be used to collect data on outcomes for the duration of the trial, particularly in phase II and III trials (6,7). Many of the initial BD4BO projects consider big data more broadly to cover both trial and RW settings.

Characteristics of outcomes collected as 'big data' may differ if they are collected in RW or trial settings. For example:

- A wider coverage of the population will be collected from big data collected in RW settings than in more narrowly defined populations typical of trials.
- More missing data is likely in RW settings – important data to contextualise outcome data (such as the patient or population demographics or characteristics of the clinical practice) may not be captured or may be captured inconsistently (7).
- Wide variation in data collected in RW settings – while trials typically have pre-planned times for collection, collection of most data in RW settings will usually occur when the patient presents, which is more likely to vary.
- Outcome measurement instruments (OMIs) used to collect data in trials may be different than in RW – in routine care settings, there may be limited time to complete detailed or time-consuming questionnaires (see also Stage 5).
- Big data may be collected through different platforms – wearable technology may mean different devices and mechanisms are used to collect data (6).
- Quality of data collected in RW settings may be lower than in trial settings which typically have carefully designed protocols for collecting data.

Big data, and linking of different sources of big data, has the potential to have a significant impact on European healthcare systems and address current issues that these healthcare systems are facing. For example, the ability to collect and link data from the same patient across different sources could address issues such as poly pharmacy and comorbidity. The collection of big data through the use of wearable technology or mobile devices could also enable patients to be more actively involved in the collection of outcomes relevant to them.

CORE OUTCOME SETS (COS)

COS have been defined as "an agreed standardised set of outcomes… [that] represent the minimum that should be measured and reported in all clinical trials of a specific condition, and are also suitable for use in clinical audit or research". (18)

The concept of COS has gained traction as a way to improve consistency in the collection and reporting of outcomes within diseases area and to ensure a focus on the patient and their experience (8). While COS initially were concentrated on clinical trials, there is an appreciation that COS have a much wider applicability, in for example RW settings (9). Different terms are used to refer to the concept of COS by different groups; various initiatives in this area and terms used are summarised in the Box below.

EXAMPLES: Initiatives with a focus on COS

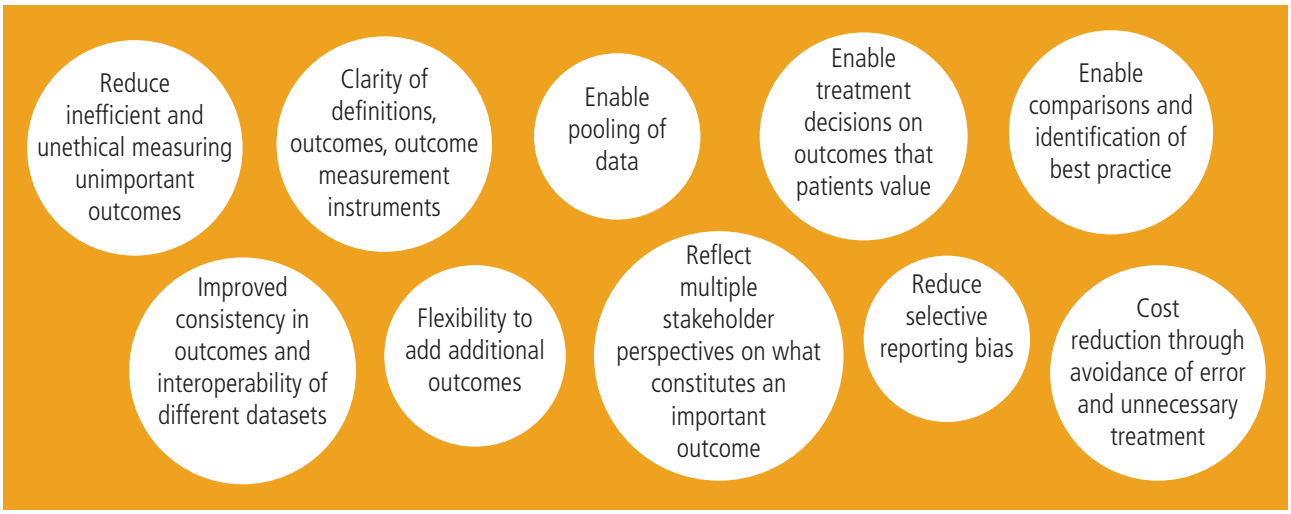
- COMET Initiative (Core Outcome Measures in Effectiveness Trials) (www.comet-initiative.org) is an international multi-disciplinary network which aims to raise awareness of current problems with outcomes in clinical trials, encourage the development of COS, and provide resources to enable the development of COS (18).
- ICHOM (International Consortium for Health Outcomes Measurement) (www.ichom.org) develops 'standard sets' of outcomes for routine or RW settings across a range of disease areas (standard sets also include minimum datasets which refers to other characteristics like age or health behaviours) (19).
- COS developers in specific disease areas include OMERACT (Outcome Measures in Rheumatology) (https://omeract.org) for rheumatoid arthritis and IMMPACT (www.immpact.org) for pain which refer to 'core domain sets' or 'core outcome domains', respectively (20,84) (additional groups can be found under 'COS Collaborative Groups' at www.comet-initiative.org/cosuptake (56).
- EMA patient registries initiative aims to address a number of challenges leading to inefficiencies and duplication of effort such as the harmonisation of data collection across disease registries (85). See www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral_content_000658.jsp
- COSMIN initiative (COnsensus-based Standards for the selection of health Measurement INstruments) (www.cosmin.nl) aims to improve the selection of health measurement instruments (86).
- The Green Park Collaborative (www.cmtpnet.org/green-park-collaborative) are leading a project working with post-regulatory decision-makers to promote uptake of COS (8).

Incorporating multiple stakeholder perspectives

The development and use of COS has many potential advantages (see Figure 1) including the ability to reflect different stakeholder needs transparently and promote evidence generation that can address needs of a wide group of stakeholders.

Incorporation of patients' perspectives in COS development, for example, can ensure that outcomes collected and evidence generated are patient-centred. It can ensure that evidence generators collect data on the outcomes recommended within a COS, that meets the needs of healthcare system decision-makers (i.e. regulators, health technology assessment (HTA) agencies and payers). As such, it has the potential to increase efficiency in the evidence development pathway for medicines and improve patient access to effective medicines. In the context of big data, the standardisation of outcomes across multiple sources enables analyses across multiple datasets generated in healthcare practice, therefore harnessing the potential of large RW healthcare data.

FIGURE 1 Potential benefits of developing and using COS

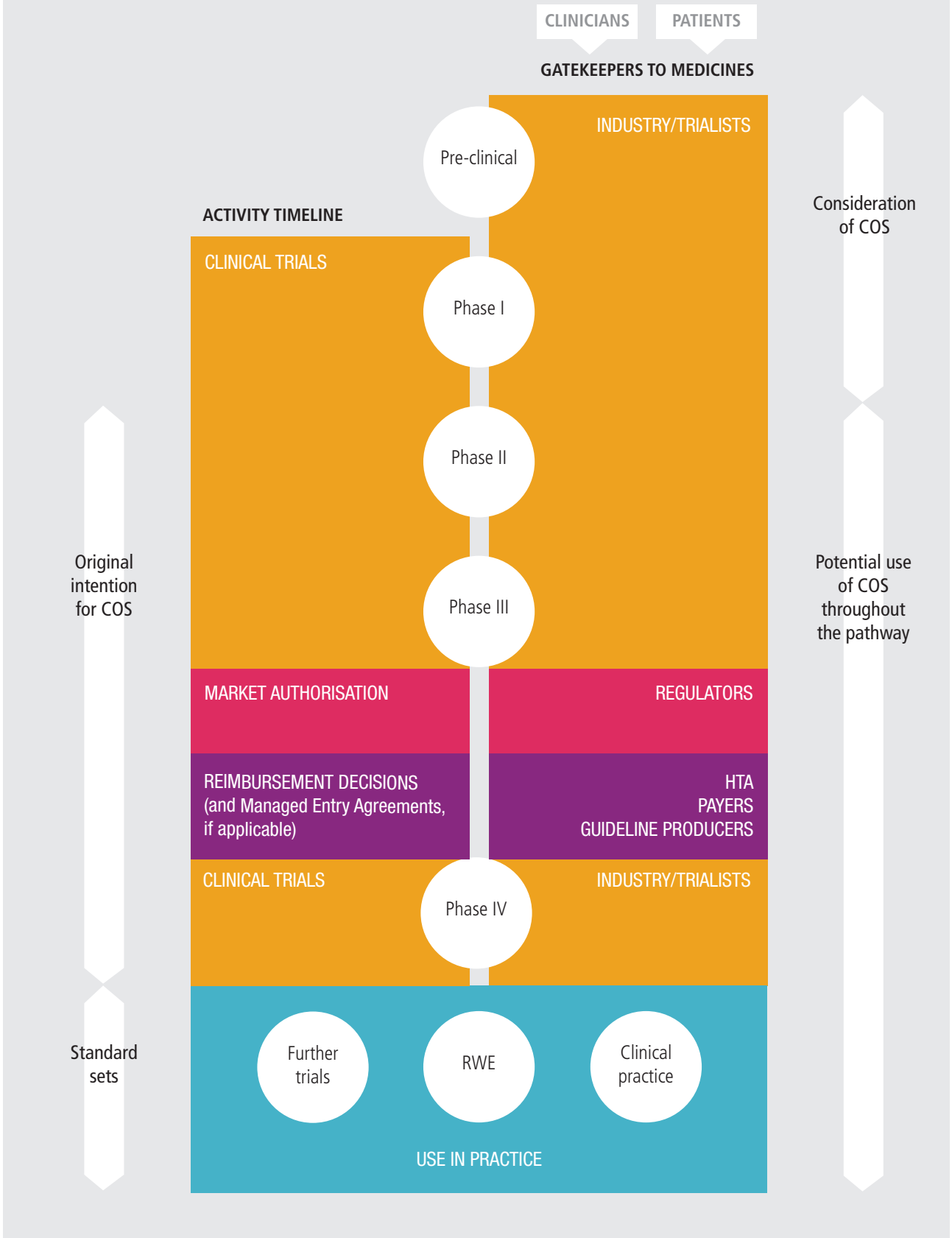


Use of COS in different settings

Currently, few COS are developed explicitly to be used across different settings such as in trials and/or in clinical practice (9,10). The development and use of COS across different RW settings could improve interoperability between different sources of data. Outcomes collected in trials, RW-settings and throughout the evidence development pathway (i.e. in early phase II clinical trials all the way through to clinical practice) could enable pooling of data or comparisons across these mixed settings and to inform healthcare system decision-making (Figure 2). This may be particularly useful with the increased use of managed entry agreements and regulatory pathways that allow accelerated marketing authorisation. Measuring as many outcomes from a COS as possible in a phase II study can also help with planning of the phase III trial.

The process of developing a COS is unlikely to differ substantially regardless of which setting it is being developed for but there may be some different practical considerations. These considerations have been highlighted throughout the stages of the process shown in Figure 2.

FIGURE 2 Outcome selection in the standard medicines development pathway



There may be variations in this pathway. For example, market authorisation or reimbursement decisions could be made earlier.

TOOLKIT STRUCTURE

The toolkit describes a suggested 6-stage approach to COS development with options to consider within each stage; however, depending upon resource and requirements, other options could be considered. An overview of the approach described in this toolkit is presented in Figure 3.

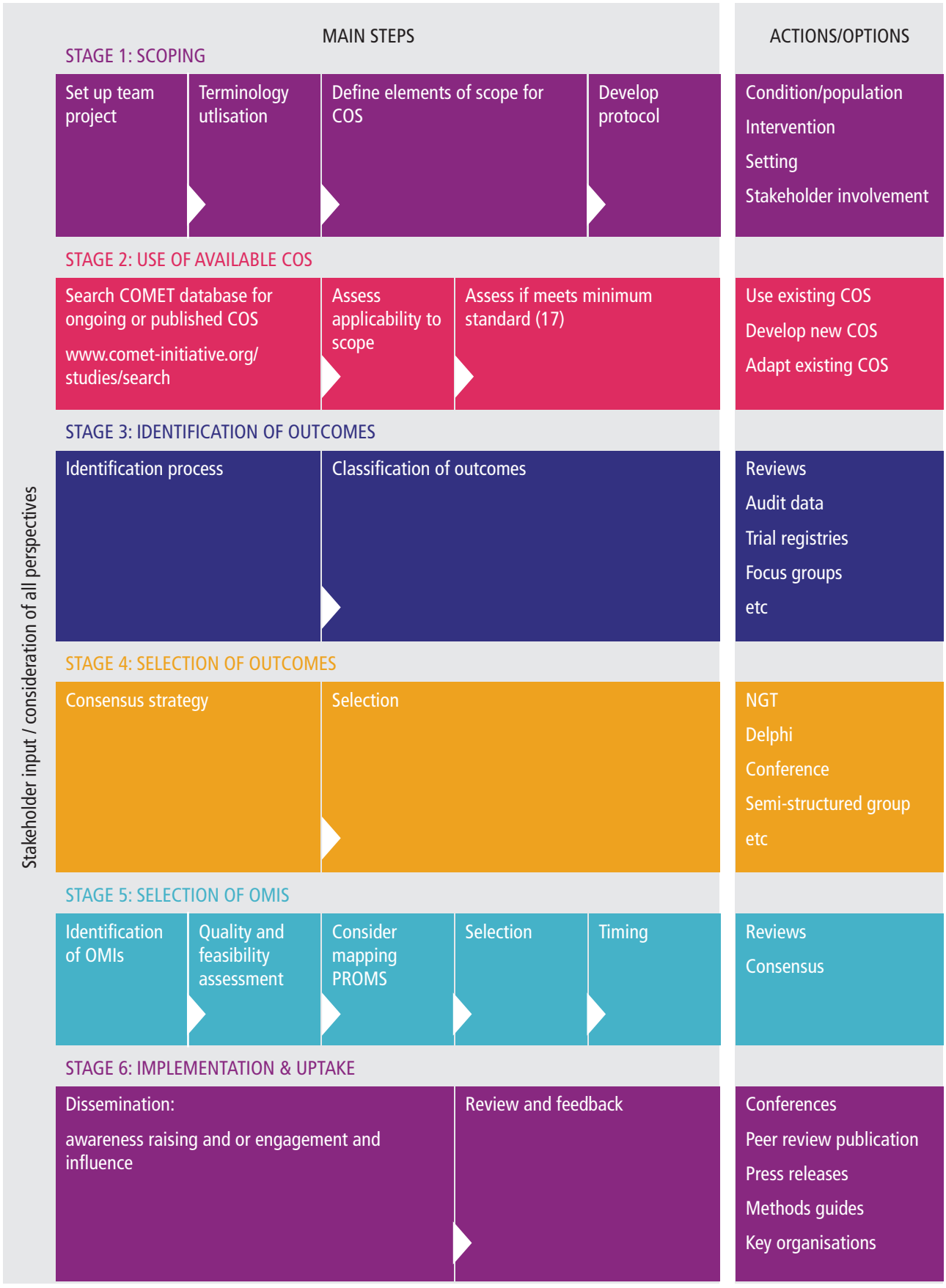
HOW TO USE THIS TOOLKIT

This document provides a stage-by-stage approach for developing a COS, from planning and scoping to identification and then implementation.

Each stage contains:

- Key questions to think about.
- Signposting to methodological options.
- Guidance notes for the practical selection of appropriate methods for a COS.
- Examples of case studies.
- Summary of key points.

FIGURE 3 Overview of stages for development and implementation of COS



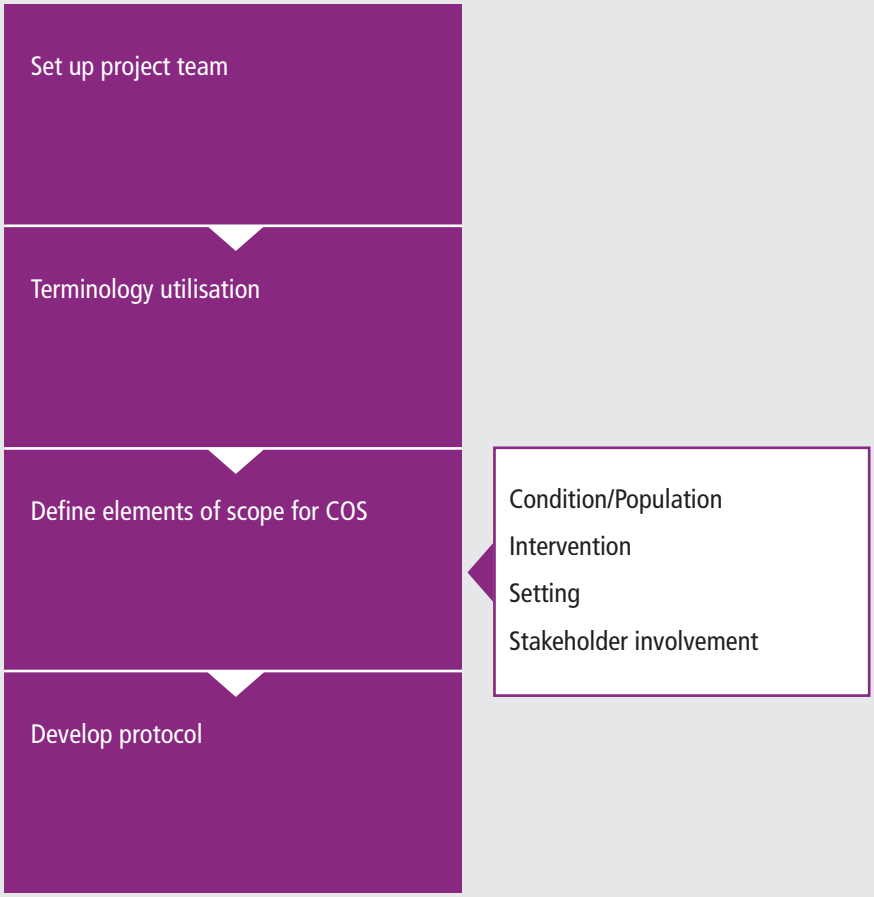
Notes: COS = Core outcome set; OMI = outcome measurement instrument.

STAGE 1

SCOPING

QUESTIONS TO CONSIDER

- Does the project team have the required key skills?
- Are responsibilities and resources defined?
- Is there representation from a number of perspectives?
- Are responsibilities and resources defined?
- Are all stakeholders using the same terminology with a common meaning?



Developing a scope for the COS a priori is good practice; a scope can ensure clarity of focus for the work and reduce the chance of misinterpretation. A number of initiatives recommend the use of a scope including COMET, HOME, and OMERACT (11–13).

SCOPING

FORMING A PROJECT TEAM

A research project lead team (or working group) can define the scope, set up the protocol which outlines the activities that will be undertaken, identify relevant stakeholders to participate, and take responsibility for providing leadership, project management and support.

The ideal constitution and size of a project team will depend on the needs of the project. Expertise and skills of stakeholders that could be important in COS development, including a project team, are summarised in Table 1. Ideally, team members should have a range of different skills and backgrounds. The geographical range of stakeholders included may vary, depending on the project. For example, BD4BO projects are specifically focused on European stakeholders. If possible, a wider geographical representation can ensure more broad perspectives are incorporated and potentially increase uptake of the COS more widely.

Once a project team is set up, each member's role and responsibility should be outlined to ensure a shared understanding. Over time, team members' roles may change from being core (fully dedicated to the research goal) to peripheral (committed to the research goal, but not as actively involved), and vice versa.

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All participating stakeholders of a COS development process need to be genuinely open to challenge, prepared to explain their reasoning and ready to reconsider their opinion in the light of a good argument.

STAKEHOLDER INVOLVEMENT

Stakeholders, beyond the project team, could be involved at any stage, including in developing the protocol, identifying outcomes, as part of the consensus group, or as a reference group to provide advice. There is no absolute rule about the number of stakeholders that should be involved. Which stakeholders should be involved and how their perspective will be incorporated will depend on the scope and the disease area for that COS.

Table 1 provides some suggestions of stakeholders and how they may be involved in the development of a COS; the 'Evidence for all' section makes some further suggestions on involvement of key stakeholders. The approach to involving stakeholders should be clearly outlined in the scope and/or protocol.

When developing COS that will be applicable in routine care or other RW settings, database or data collection managers who can advise on feasibility of collecting outcomes in these settings could be involved.

TABLE 1 Suggestions for stakeholders that could be involved in COS development

Stakeholder perspective[1]	Unique contributions/expertise	Potential level of input			
		Member of project team	Identify important outcomes (Stage 3)	Consensus group (Stage 4)	Reference group (at any stage)
Patients[2] For more about involving patients see the 'Evidence for All' section (page 40)	Participation by providing personal experience of a condition or treatment. Involvement by helping set priorities and/or designing the process including assisting in developing postal and online questionnaires to ensure the questions are meaningful to the target patient population and written in appropriate language (14)	✓	✓ (i.e. using qualitative research)	✓	✓
Clinicians with expertise in the disease area	Insights into the disease area and experience with the patients and their experiences.	✓	✓	✓	✓
General practitioners	May have insights into practical considerations on collection of specific instruments such as burden for the collector of the data. As they may collect some of the data, it can also help to achieve buy-in with this stakeholder group.	Depending on disease area	✓	✓	✓
Academics/ clinical researchers[2]	May have 'methodological or content expertise such as outcome measure development, biostatistics, psychometrics, qualitative studies, comparative effectiveness and clinical trial design' (13).	✓			
Qualitative researchers	Expertise in designing and conducting qualitative research, such as use of interviews, focus groups, etc if planned.	✓	✓		✓
Regulators, HTA agencies, payers See 'Evidence for all' (page 37)	Identify outcomes that are important to their decisions; use of these outcomes in COS can help ensure the right evidence is collected for these decision-makers' needs.		✓	✓	✓
Industry See 'Evidence for all' (page 42)	Key evidence generator		✓	✓	✓
Data collection managers/ quality controllers	As collectors of the data, may be able to offer input on feasibility of data collection or other important considerations. May be particularly useful for COS developed for RW settings.	✓	✓	✓	✓

1. The COMET handbook provides recommendations regarding setting up a study team and study committees
2. Patients can include individual patients or carers, patient advocates, patient organisation representatives or patient experts (15).

STAGE 1

SCOPING

Common terms in outcomes research to define in advance

- Outcome
- Endpoint
- Clinical outcome
- Safety/adverse event
- Resource outcomes
- Surrogate outcomes
- Intermediate outcomes
- Composite outcomes
- Outcome measure
- Real-world evidence
- Real world setting
- Routine care
- Biomarker

'WHAT IS AN OUTCOME?' USEFUL TERMS TO DEFINE UP FRONT

When working across diverse stakeholder groups it is important to ensure all are using terms consistently. It is not uncommon for terms to have different meanings in different settings (across disciplines, countries and organisations) (appendices A and D).

Definitions for key terms should be agreed in advance to avoid confusion before engaging with wider stakeholders and project participants. Consideration should also be given to particular terms in the disease area (and clinical term usage) to ensure all stakeholders have a shared understanding (Stage 3).

Common definitions for some non-disease specific terms can be found in the Glossary. Some common terms that may have different meanings among different stakeholder groups and should be considered for definition at an early stage are listed in the panel (left).

DEFINING A SCOPE A PRIORI

The scope should describe the criteria covered in Table 2 (11).

TABLE 2 Criteria to be included in the scope for a COS

Criteria in the scope	Key questions to consider
Condition/population The disease area, population or sub-population that the COS will apply to.	• What is the specific health condition of interest? Are all classifications and stages of condition going to be included? • What is the population of interest? Are all ages and subgroups included in the target population? • Is this population difficult to measure outcomes in (i.e. children, people with learning disabilities)?
Intervention A COS designed to be used for any intervention may be different for a COS developed for a particular type of intervention. For example, a COS developed for a specific class of medicine may include an adverse event associated with the medicine, but this adverse event may not be a particular concern when a device is used for the same condition.	• Is the COS focussed on a specific type of intervention (i.e. medicines only or a specific type of medicine) or will it apply across all types of interventions?
Setting Where the COS will be utilised such as in clinical trials, research and practice as well as RW settings such as registries.	• Is there a particular setting that the outcome and outcome measures are to be utilised in?

SCOPING

STAGE 1 KEY POINTS

- A project team can define the scope, protocol, identify relevant stakeholders, and take responsibility for providing leadership, project management and support.
- Key terms should be defined to facilitate shared understanding.
- A scope should be developed which covers the intended condition/ population, intervention and setting; it could also outline which perspectives will be taken into account.
- A protocol, based on the scope, should outline the intended approach to developing the COS, based on the resources available (see checklist); it should also specify when and how different perspectives will be taken into account.

DEVELOPING A PROTOCOL A PRIORI

Preparing a protocol helps to improve transparency and communication, the use of a protocol can enable stakeholders to agree the process and strategy.

As with most research, developing a protocol a priori is good practice as it can prevent potential biases, improve transparency, ensure communication with others, and enable relevant stakeholders to agree the process and strategy (11).

The protocol should take into consideration the available resources. A number of initiatives recommend the use of a protocol including COMET, HOME, and OMERACT (11–13).

PROTOCOL CHECKLIST

- ✓ Check if it is possible to use or adapt an existing COS which addresses the scope (see Stage 2).
- ✓ Check for any ongoing projects developing COS in the same disease area; developing sets collaboratively can reduce duplication of work. Search for 'protocol' at www.comet-initiative.org/studies/search (16).
- ✓ Look at examples of protocols for developing COS on the COMET website at www.comet-initiative.org/resources/studyprotocols (87)*.
- ✓ Plan timelines and allocate resource capacity/roles.
- ✓ Plan involvement of stakeholders (see 'Stakeholder involvement' page 10).
- ✓ Consider using the minimum standards set out in the COS-STAD guidelines during development (17). This includes pre-specifying scoring systems, consensus definitions if formal consensus is planned, criteria for dropping and adding outcomes, and plans for addressing attrition bias (see Stage 4).
- ✓ Consider consulting on the protocol with a reference group and stakeholders. Draft versions of protocols should be written in a way that is accessible to all stakeholder groups.
- ✓ Make the trial protocol publically available, either in the COMET database www.comet-initiative.org/contactus/submitnewstudy (88), in PROSPERO www.crd.york.ac.uk/PROSPERO (89) if a systematic review is planned, or through a journal publication.
- ✓ Consider developing an implementation plan early on (see Stage 6).

* There is currently no gold standard on writing a protocol for developing minimum outcome sets; standards for developing protocols are currently being developed in the Core Outcome Set-STAndards for Protocols (COS-STAP) project (COMET, personal communication).

STAGE 2

USE OF AVAILABLE COS

QUESTIONS TO CONSIDER

- Is there already a COS that could be used or adapted?
- How do I assess the usability of a published set?
- Can adaptions be made to sets that are already available to factor in real world settings?

Search COMET database for ongoing or published COS

www.comet-initiative.org/studies/search

Assess applicability to scope

Assess if meets minimum standard (17)

Develop new COS

Use existing COS

Adapt existing COS*

Important!

Any processes for adapting or modifying COS must be clearly described'

Scope population/intervention differs:

Consider consulting an abridged panel of experts/stakeholders.

Scope setting differs (i.e. trials to apply to RW settings):

Consider assessing feasibility, time, resources for RW setting. Consider conducting mapping activity from COS to RW sources.

Needs update (i.e. side effects of new agent):

Consider consulting with an abridged panel of experts/stakeholders.

* If considering extensive adaptation, consider contacting authors of previous COS to investigate potential for collaboration

USE OF AVAILABLE COS

It is best practice to first consider if there are any available COS in the disease area that could be used or adapted rather than developing a new COS. The freely available COMET database (www.comet-initiative.org/studies/search) can be used for this purpose (9,10,16).

It is best practice to explain the decision to use or adapt an existing COS, or to develop a new COS. The rationale and process for adapting an existing COS should be clearly described in a protocol.

COS-STAD recommendations to improve the quality of COS development (17)

Scope – the research or practice setting(s) in which the COS is to be applied, the health condition(s), population(s), and intervention(s) covered by COS.

Stakeholder involvement – those who will use the COS in research, healthcare professionals with experience of patients with the condition, patients with the conditions or their representatives.

Consensus process – initial list considers clinical & patient views, a priori specifications of consensus definition and processes, efforts to reduce ambiguity in language.

ASSESSING THE APPLICABILITY AND USABILITY OF EXISTING COS

An existing COS should be considered for its applicability and usability against the scope of the work. While there is no current gold standard for assessing the quality of an existing COS, the Core Outcome Set-STAndards for Development (COS-STAD) (17) (see panel) may facilitate an assessment of the methodological robustness of an existing COS and aid in making a subjective judgement about whether a COS can easily be adapted (Case study 1).

If more than one COS exists, a subjective judgement about which (if any) are applicable and usable should be made.

CASE STUDY 1 Application of minimum standards to existing COS

In the DO IT project, the 11-item COS-STAD recommendations were applied to studies retrieved from the COMET database for the first 4 disease areas addressed in BD4BO projects (Alzheimer's disease (AD), haematological malignancies (HM), cardiovascular disease (CVD) and prostate cancer) (17).

The study found that all published COS met the scoping criteria.

Regarding involvement of stakeholders in COS development, few studies incorporate the patient's perspective into COS development.

The 4 COS-STAD recommendations regarding the consensus process were not addressed by most of the studies; however, this may due to poor reporting. This was particularly evident from studies on COS for HM, this could be due to many of the studies being older (published before 2000) rather than a feature of the disease area. Studies that are more recent tended to meet more minimum standards.

The application of COS-STAD recommendations is encouraged for any future studies developing COS. The use of COS-STAD facilitates the assessment of COS by researchers and clinicians.

A more detailed description of this work can be found in appendix B.

ADAPTATIONS TO COS FOR REAL-WORLD SETTINGS

The majority of COS have been developed to be used in clinical trials (9). In order to reduce duplication of effort, and as BD4BO projects are interested in RWD sources, existing COS could be adapted to make them applicable in

USE OF AVAILABLE COS

STAGE 2 KEY POINTS

- Before starting the development of a new COS, the possibility of adapting existing COS should be considered to reduce duplication of effort.
- There are no gold standard methods for assessing existing COS or adapting existing COS; however judgements can be made about the applicability and adaptability of a COS.
- If resources are available, those adapting existing COS to RW settings could consider mapping outcomes recommended in the COS to consider practicalities of collecting the outcomes recommended in COS and to identify gaps in data collection to be addressed.

RW settings. Studies with COS for RW settings may include outcomes that are more easily tracked in clinical practice, through routinely available data sources or through newly designed data collection efforts. However, there is little agreement and few examples to date of how existing COS developed for trial settings could be applied or adapted for RW settings.

COS developers need to consider carefully what outcome categories and outcomes are required versus the type of available data and, if needed, adapt the COS to make the COS useful for the specific purpose.

An additional factor that should be considered if adapting COS for RW settings includes consideration of the timing of outcome measurements in sources which potentially will be different from those used in trial settings which usually have pre-defined and finite measurement points.

As part of the IMI DO→IT initiative, researchers have investigated the potential for collecting outcomes recommended within existing COS in RW settings (Case study 2); they found that certain outcomes recommended to be measured in COS were available in RW settings but there were gaps. Developers of COS for RW settings who wish to use or adapt existing COS should consider this possibility and perhaps undertake a similar mapping process to consider the practicalities of collecting the outcomes recommended. However, it can be time-consuming activity so this should be considered against the potential added value.

CASE STUDY 2 Mapping outcomes from existing COS to RWD sources

A team of DO→IT researchers conducted a 'mapping exercise' to determine whether and how the outcomes in COS for 4 disease areas (AD, HM, CVD and prostate cancer) were measured in known RWD sources. This included administrative databases, disease registries and electronic medical records or electronic health records. The aim was to examine the potential of applying published COS in RW settings. The study also considered outcome definition, timing of measurement and type of measurement instrument (e.g. laboratory or imaging data, patient-reported).

The outcomes reported in COS for CVDs were – to some extent – captured in the examined sources, apart from patient-reported outcomes and other outcomes such as time to re-occurrence which may need to be derived from multiple variables. For AD, there were some outcomes collected in RW sources but other important outcomes such as carer burden, patient behaviour, adverse events, and health economic measures were not. For the oncological conditions, there were more COS outcomes collected, but often not quality of life.

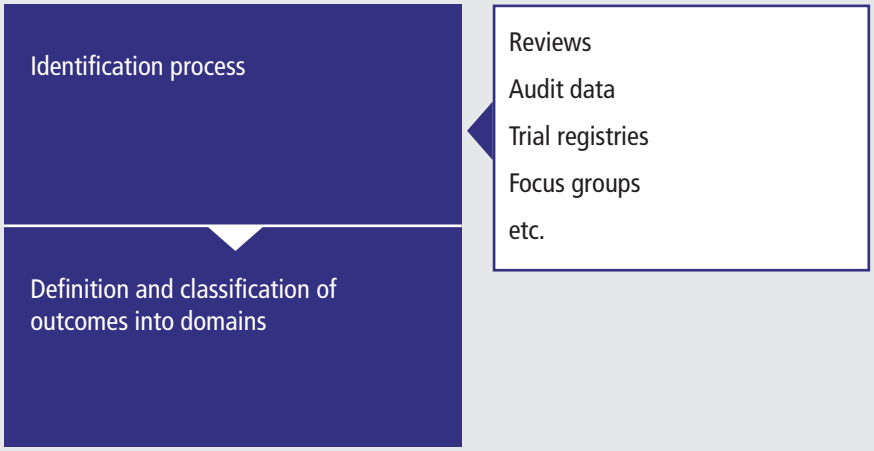
Whilst only areas were considered and findings may differ for different RW sources in different disease areas, this exercise demonstrates some challenges for collecting data for existing COS outcomes in real-world studies currently. More research is needed. A more detailed description of this work can be found in appendix B.

STAGE 3

IDENTIFICATION OF OUTCOMES

QUESTIONS TO CONSIDER

- What are some options for identifying outcomes to consider including in a COS?
- How could outcomes important to key stakeholders be identified?



This section introduces and outlines methods and practical considerations to help identify outcomes appropriate for a disease area. This list can then be used as a source for the selection process in Stage 4.

Aside from potentially including stakeholders involved in the collection of RWD this process is unlikely to differ between trial and RW settings. The outcomes included in a COS also may be similar in different settings but the instrument used to measure them may differ due to feasibility (see Stage 5).

IDENTIFYING A COMPREHENSIVE LIST OF OUTCOMES

A selection of options and mechanisms for identifying outcomes are described in Table 3. Some of the methods are promoted or used by a number of groups including COMET, ICHOM and OMERACT (18–20).

A combination of methods or variations of options could be used, to ensure that all important outcomes are identified. For example, a literature review could be a starting point, though previous literature may not reflect all outcomes important to patients so additional work such as qualitative research to identify these could be very beneficial. The decision about which approach to use may need to weigh the available option(s) with the resources available.

For a description of the approach ROADMAP are using to identify important outcomes in Alzheimer's disease see Case Study 3.

CASE STUDY 3

Identifying important outcomes – experience from ROADMAP

The ROADMAP project has conducted a systematic review (90) of both published and unpublished studies identifying outcomes considered both important and relevant to Alzheimer's disease as well as criteria for disease progression (91). They found 34 studies examining perspectives of stakeholder groups.

This work will be supplemented by additional work to define a priority set of outcomes which will include surveys and workshops. An interim summary of this work has been published (92).

https://roadmap-alzheimer.org

TABLE 3 Options for identifying outcomes

Pros	Cons	Sources / references	Possible variations if less resource
Existing COS identified in Stage 2			
Pragmatic approach.	Unlikely to be comprehensive.	As per stage 3, COMET database (16)	
Conduct a systematic review of peer-reviewed published studies including clinical trials or qualitative studies*			
Systematic approach. Likely to have up-to-date outcomes.	Time-consuming. May not capture what outcomes are important to all stakeholders.	Cochrane (22)	Consider date restriction. See next option.
Systematic reviews in the area			
Less time consuming than conducting a new review.	May not capture more recent outcomes. May not capture what outcomes are important to all stakeholders.	Common databases such as Medline, CINAHL, Embase, Cochrane Database of Systematic Reviews, PsycINFO. (23–27)	Consider only recent reviews (date restriction).
Existing RW sources including clinical audit, EHR, registry data in the disease area, claims databases			
Useful when developing COS for these settings to see what are already collected in these settings. May indicate outcomes that are practical to collect.	May be difficult to determine outcomes collected for some sources. May not capture what outcomes are important to all stakeholders.	Cross-border Patient Registries Initiative (PARENT) 'registry of registries' (lists over 200 patient registries across Europe) (28) AHRQ Registry of Patient Registries (RoPR) (29)	
Conduct primary qualitative research with key stakeholders particularly patients (i.e. surveys, interviews or focus groups)			
Elicit views of key stakeholders which may not be captured in outcomes in available trials, particularly patients (103).	Time consuming. Requires skilled researchers to facilitate the work. If used to gather patient views, patient participants do not necessarily need to understand COS concepts; they can describe their experiences using their own language (14).	Qualitative methods (30) Social research methods (31) COMET PoPPIE (32) ICHOM (33)	Look for existing qualitative research with these stakeholders. Set up an advisory group.

* Systematic reviews can also be used to identify outcome measurement instruments (OMIs; see the Glossary) (Stage 5).

TABLE 3 Options for identifying outcomes (continued)

Pros	Cons	Sources / references	Possible variations if less resource
Request important outcomes from key opinion leaders in the field			
More simple approach than others.	Not formal qualitative research. May not capture a wide-range of views. Likely to reflect status quo.		
Review publicly available documents from regulatory and HTA bodies in the same or a similar disease area			
Ensures outcomes important to these stakeholders can be included.	Assessments in the disease area may not be available. May be time-consuming as information on outcomes may not be easy to find in some HTA reports. Examining one HTA agency may not indicate what is important to all HTA agencies (see also 'Evidence for all')	EMA website to access European Public Assessment Reports (EPAR) (34) EMA disease-specific guidance (35) To determine if an HTA organisation has publicly available assessments see EUnetHTA 2017 report, Annex 1, pp. 32–33 (36)	
Other including clinical trial protocols			
May include up-to-date outcomes.	Could be time-consuming with little additional benefit to conducting systematic review.	clinicaltrials.gov (37) EU Clinical Trials Register Aggregate Analysis of Clinicaltrials.gov (AACT) (38)	

IDENTIFICATION OF OUTCOMES

STAGE 3 KEY POINTS

- A number of options can be used to identify outcomes; the choice depends on what is appropriate for a disease area and available time and resource.
- Examination of outcomes currently collected in RW settings is an important source of information, particularly when developing COS to be applied in these settings.
- Outcomes which are relevant to all stakeholders in a disease area, not just what has been used previously, should be explored.

DEFINITION AND CLASSIFICATION OF OUTCOMES

Once a comprehensive list of outcomes has been identified, it may need to be prepared for the selection exercise in Stage 4.

- **Clear definition of outcomes for multiple stakeholders:** all stakeholders need to understand what each outcome means. The wording should be easily accessible and understandable to a wide range of stakeholders. Additionally, it may be helpful to include precise lay and clinical definitions of each outcome, possibly including both, for example, using the lay term heart attack instead of myocardial infarction. Clear wording and use of definitions may also avoid unnecessary revisions during any consensus processes used in Stage 4.
- **Use of domains to classify outcomes:** to ensure there is no repetition of outcomes within the list for the consensus process, duplicates or overlapping outcomes should be checked. It may help to categorise outcomes into domains. The use of domains can also help provide structure to the outcome selection process; there are a number of existing theoretical or conceptual frameworks which can be considered (21). Development of new domains requires qualitative research or at least consultation with key stakeholders including patients.

Think about including quality of life (QoL) and longer-term outcomes in a COS if looking to generate evidence for market access.

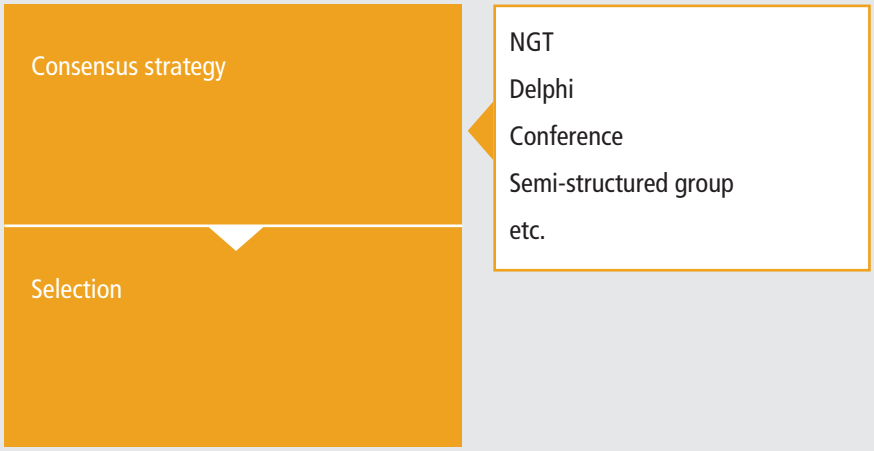
QoL is considered to be essential to HTA decision-making and is considered important to regulators; longer-term outcomes are also preferred by HTA agencies. (appendices A and D).

STAGE 4

METHODOLOGY FOR COS SELECTION

QUESTIONS TO CONSIDER

- What are some methodological options or approaches to agree outcomes?
- Are different methods suitable for all stakeholders?
- Should meetings with the group be face-to-face, by teleconference or online?
- What sample size of each stakeholder should is sufficient?
- What response rate / level of attrition is acceptable?
- What level of agreement constitutes a majority or 'consensus'?



Some methods that can be used to select or agree on outcomes in a COS are summarised in Table 4. A combination of these methods can also be used. For example, a Delphi survey can be combined with a semi-structured group discussion or a workshop with a web-based consultation. The suitability of the methods used may vary by stakeholder group and disease area. For instance, a Delphi survey may not be suitable for some patients such a those with early stage dementia. In this situation, interviews might be a more fruitful method to elicit patient views (11).

Some of the methods described in Table 4 are promoted or used by a number of groups including COMET, ICHOM and OMERACT (18–20).

EXAMPLE ICHOM process for selecting outcomes

Initiatives like ICHOM have developed their own pre-defined standardised process to select outcomes (19). This process involves convening a working group for 8 teleconferences that each focus on one specific aspect of the 'standard set' development, for example, a discussion on the outcome domains to include. Proposals are developed based on literature, input from patient representatives and advice from expert panels to guide these teleconferences. Following each teleconference, the working group votes via online survey. This may be a single round of voting or a 3-round Delphi voting process.

TABLE 4 Methodological options for selecting COS

Details	Pros	Cons	Further resources
Semi-structured group discussions (workshops, meetings, round table discussions)			
Involving clinicians/experts who use these measures can allow participants to ask specific questions about outcomes. May involve a formal voting process. No universally defined format.	Relatively quick and easy to implement. Can address stakeholder queries and concerns. Can incorporate domains considered important by stakeholders in a structured manner.	Consensus process can be ambiguous if formal voting process not incorporated. Consensus definition will vary based on how group discussion is organised. May be difficult to obtain sufficient attendance at a face-to-face conference.	Systematic review reporting methods used to select outcomes (10)
Unstructured group discussions (task force, committees, panels)			
Members may be selected for expertise and recommendations presented following general discussion. Less common for developing COS. Can use semi-structured format.	Quick and easy to implement.	High likelihood of not incorporating all stakeholder perspectives. High likelihood of not considering key domains. Consensus process ambiguous.	Systematic review reporting methods used to select outcomes (10)
Consensus development conference			
Participants selected for their expertise within a disease area invited to a conference to produce a consensus statement. Specific format and conduct varies.	Relatively quick and easy to implement in comparison to use of formal consensus methods (nominal group technique or Delphi).	Specific format and conduct vary widely. May be difficult to obtain sufficient attendance at a face-to-face conference.	Format and conduct of consensus development conferences (39)
Nominal Group Technique (NGT)			
Structured variation of small-group discussion to reach consensus. A moderator poses questions to the participants and then asks the participants to prioritise the suggestions and ideas of all group members.	Structured and methodologically rigorous process. Generates a greater number of ideas that traditional group discussions. Prevents one person from dominating the discussion. Allows the group to prioritise ideas democratically by voting. Can be used to ensure a wide, transparent and anonymous patient participation in contrast to the sole use of qualitative research to involve patients (14).	Requires significant preparation and planning. May minimise discussion which could prevent the full development of ideas.	Evaluation briefs – Centre for Disease control and Prevention (40).

TABLE 4 Methodological options for selecting COS (continued)

Details	Pros	Cons	Further resources
Delphi			
Solicits the opinions of experts through a series of carefully designed sequential questionnaires interspersed with information and opinion feedback. Questionnaire responses are summarised, fed back anonymously in subsequent questionnaire, giving participants opportunity to consider views of others and change their opinions. Can be conducted virtually.	Structured and methodologically rigorous process. Prevents one person from dominating the process. Allows reconciliation of differing views and opinions. As it does not need to be conducted face-to-face, it can reduce travel times/costs, allow anonymous and confidential responses and generate consensus from geographically dispersed group of stakeholders. Can be used to ensure a wider patient participation in contrast to qualitative research (14).	No universal guidelines on methodology (e.g., definition of consensus, scoring system, number of questionnaire rounds). Time delays between rounds of questionnaires. Longer process may result in high levels of attrition and attrition bias.	The Delphi method – RAND Corporation (41). The COMET Handbook (11).
Mixed methods			
Varies, depending on which methods are chosen.	Best of both worlds – more room for ideas to be developed but can have a structured process to eventually develop consensus. Can methodologically establish scope of outcomes under consideration prior to developing the COS.	Time consuming. Costly. No universal guidelines on methodology.	Systematic review reporting methods used to select outcomes (10).

METHODS FOR SELECTING OUTCOMES IN RW SETTINGS

There is currently no definitive guidance as to whether methods for developing COS for clinical trials should be different to developing COS for RW settings. The type of participants involved in COS development could be slightly different for those developed to be applied in RW settings (i.e. database manager); however, the actual methods for developing COS are unlikely to differ substantially. More research is needed regarding whether the methods should be differ by setting.

DEFINITION OF CONSENSUS

There is no universal definition of what constitutes a majority consensus. For example, a variety of scoring processes can be used in the Delphi process, such as the Likert scale (a multi-point grading system based on level of importance given to an outcome), ranking of outcomes, and the allocation of points from a pre-specified fixed amount.

One consideration when deciding on a consensus definition is how stringent or relaxed it should be – criteria that are too relaxed may lead to a long list of outcomes and criteria that are too stringent may not include key outcomes.

Some published COS development studies link the consensus definition to the scoring process – i.e. based on means, medians or percentage of participants identifying an outcome as important. An assessment of COS found that the methodological criteria for these have rarely been justified in previous research or defined a priori, and studies have adopted their own definitions of consensus (11).

EXAMPLES Consensus definitions

- The ICHOM process requires a domain to be ranked highly by at least 80% of participants in order to be included in a 'standard set' (93).
- The 70/15% consensus definition (70% of participants think an outcome should be included in a COS and only 15% consider it to be of little importance) has been recommended, based on the principle that an outcome should be included in a COS if a majority consider it to be important and only a minority regard it as having no importance (94). This consensus definition has been used in previous studies (95–97).
- The HOME group require that consensus is reached when less than 30% of participants disagree (12).

METHODOLOGY FOR COS SELECTION

STAGE 4 KEY POINTS

- There are a variety of different methods that can be used to agree outcomes; the methods chosen will depend on the time and resources available and the pros and cons of each option.
- Methods may not differ between selecting outcomes for COS that in real-world and in trial settings.
- There is no universal definition of what constitutes a majority consensus, an acceptable response rate or level of attrition, or optimum sample size or panel composition to agree outcomes.

FACE-TO-FACE VS VIRTUAL MEETINGS

Consider whether meetings should be face-to-face or virtual. Online or virtual meetings may allow more participants to be involved while face-to-face meetings may facilitate discussions increasing the ability to come to consensus in less time (9).

RESPONSE RATES / ATTRITION

There is no universal agreement about what response rates or level of attrition is considered acceptable. If attrition rates are too high and are resulting in attrition bias, measures should be taken to increase the response rate. Measures could include aligning meetings with other relevant conferences or meetings (9).

ENSURING A REPRESENTATIVE VIEW

There is no empirical evidence on the optimum sample size or panel composition for each stakeholder group; it is often a pragmatic choice made by the COS developers based on the disease area, specific stage of the disease and resources available. Considerations related to stakeholder involvement are addressed in Stage 1.

Consider how the views of different stakeholders are combined in the consensus generation process. If all individual stakeholder views considered within a single panel have equal weighting, an average of the views may favour stakeholder groups with a bigger representation.

Options to deal with this situation where differing views are expected include:

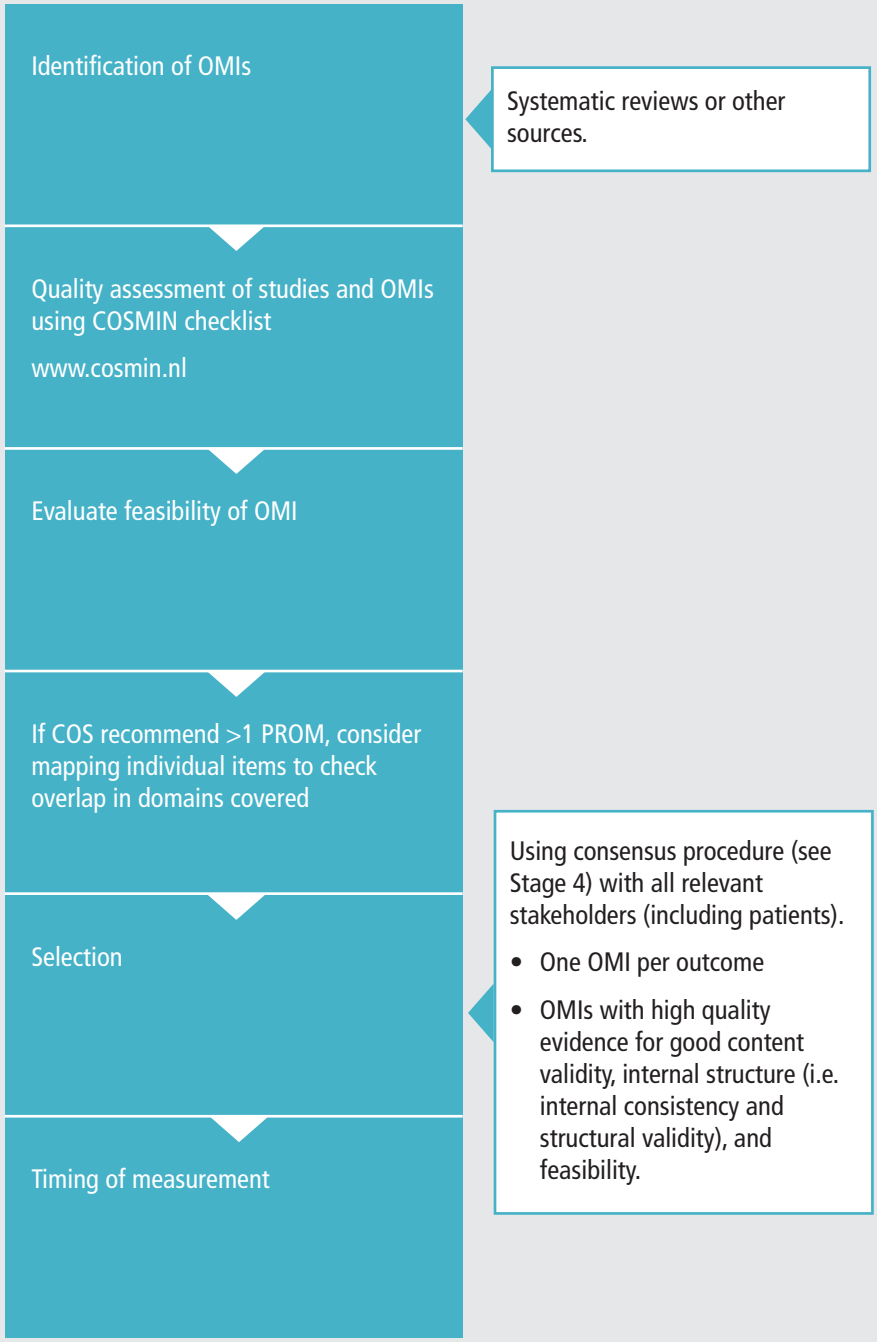
- Use of multiple panels with distinctive stakeholder groups (42).
- Weighting of views by stakeholder type but there is currently no guidance about the ideal method for weighting views (11,13). Q methodology could be used as an exploratory method to help identify groups of participants with different views (13).

STAGE 5

SELECTION OF OUTCOME MEASUREMENT INSTRUMENTS

QUESTIONS TO CONSIDER

- What steps could be taken when selecting outcome measurement instruments (OMIs)?
- What is a good OMI?
- What could be considered when selecting OMIs for COS in RW settings?
- What could be done if no instrument is assessed as having good measurement properties or does not meet feasibility criteria?



STAGE 5

SELECTION OF OUTCOME MEASUREMENT INSTRUMENTS

BOX 1 Published guidelines for selecting OMIs

- COSMIN Initiative (86)
- OMERACT handbook (13)
- Harmonizing Outcome Measures for Eczema (HOME) Roadmap (12)

Similar to the selection of outcomes, there has been methodological progress for selecting outcome measurement instruments (OMI) (Box 1). While the outcome is **what** to measure, the OMI is **how** the outcome should be measured.

The process for identifying and selecting OMIs is typically similar to that for outcomes in a COS with additional steps pertaining to measurement properties and feasibility.

QUALITY ASSESSMENT OF AN OMI

All OMIs should be assessed for quality including clinical rating scales, imaging tests, laboratory tests, and patient-reported outcomes (PROMs).

COSMIN guidelines identified nine measurement properties considered relevant for quality assessment of candidate instruments (Table 5). COS developers should consider feasibility aspects including patient's comprehensibility, interpretability, and ease of administration (43).

TABLE 5 Definitions of measurement properties

Criterion	Definition
Content validity (including face validity)[1,2]	The degree to which an instrument measures the construct(s) it purports to measure
Internal consistency[1]	The degree of the interrelatedness among the items
Structural validity[1,2]	The degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured
Reliability[3]	The degree to which the measurement is free from measurement error
Responsiveness[3]	The ability of an instrument to detect change over time in the construct to be measured
Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
Hypotheses testing	The degree to which the scores of an instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the instrument validly measures the construct.
Criterion validity[3]	The degree to which the scores of an instrument are an adequate reflection of a 'gold standard'
Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted instrument are an adequate reflection of the performance of the items of the original version of the instrument

Source: table adapted from (44) and (43).
1. COSMIN considers as the top three important properties;
2. Properties falling under the 'truth' criterion in the OMERACT filter;
3. Properties falling under the 'discrimination' criterion in the OMERACT filter (45).

SELECTION OF OUTCOME MEASUREMENT INSTRUMENTS

OMERACT has promoted the use of its 'filter', through which candidate instruments would have to pass in order to be recommended (46). The OMERACT filter consists of three component criteria, for which a question each needs to be answered to pass through:

1. **Truth** (capturing face, content, construct and criterion validity): does the instrument measure what it intends to measure? Is the result unbiased and relevant? (note: these requirements are also captured by COSMIN measurement properties - content validity, including face validity; structural validity; criterion validity).

2. **Discrimination** (capturing reliability and sensitivity to change): does the instrument discriminate between situations that are of interest? (note: these requirements are also captured by COSMIN measurement properties - reliability; responsiveness)

3. **Feasibility**: can the measure be applied easily, given constraints of time, money, and interpretability?

The filter was recently updated, but its core components remain the same and provide the guiding questions to select OMIs, as described in the OMERACT handbook (13).

FEASIBILITY OF AN OMI

In addition to the **criteria of good measurement properties** (Table 5), COS developers aiming to recommend OMIs for routine use should consider the **feasibility** of using these instruments. This is particularly important in RW settings. For example, there may be limited availability of dedicated staff to collect and enter data, patients may be unwilling or unable to extend their routine visit for additional measurements, and collection may be costly. More considerations that are important to make when selecting OMIs in RW settings are covered in Table 6.

Feasibility issues could be avoided through the involvement of additional stakeholders in the COS development process. For example, feasibility aspects of data collection are likely to be a key concern to those carrying the burden, i.e. patients and health care professionals. For COS with an international scope, involvement of stakeholders from countries with different resource endowment and contexts can act as a sense check for the feasibility of using proposed measures in other settings.

PROMS

Patient-reported outcome measures (PROMs), a type of OMI, are increasingly in the focus of health researchers and decision-makers. The criteria of measurement properties and feasibility described for other OMIs also apply to PROMS. However, **feasibility** is particularly important for PROM selection, since they require active responses from patients, can have different administration modes, and can be subject to intellectual property rights. Table 6 indicates specific concerns for the selection of PROMs.

Think about including both disease-specific and generic quality of life (QoL) instruments in a COS if looking to generate evidence for market access in different European jurisdictions as preferences for these instruments vary by decision-maker.

Regulator and HTA agency preferences for quality of life instruments are described further in appendices A and D.

TABLE 6 Feasibility considerations for selecting OMIs by importance to RW settings and PROMs

Consideration	Notes	Importance for: RW COS	Importance for: PROMs
Quality of data	Definitions and detailed instructions for testing might need to be given to ensure comparability across individual centres. For example, developers of a COS for asthma control in trials and routine care specified that lung function measurements in primary care should be performed by trained personnel and actual values of the test be recorded, rather than a statement of 'normal' or 'abnormal' (47). For PROMs, consider the planned administration mode: paper-based, over the phone, via computer or smart devices. Flexibility in how the OMI can be administered may be desired, but validity of different administration modes, including novel smart devices, needs to be established. To reduce measurement error, standardised administration of the questionnaire is desirable and can include instructions for instrument completion, such as specific time for filling out the questionnaire, maximum time allowed, and number and type of reminders sent to patients.	++	++
International perspective	In addition to cross-cultural validity (see measurement properties above), COS with international scope need to take the reality of local infrastructure into account when recommending instruments. OMIs that are part of routine practice in one country might only be available in highly specialised centres in another. For PROMs, consideration should also be given to the availability of validated translations of the questionnaire, which should incorporate language and local contextual factors.	++	++
Burden of data collection for patients and health care professionals	COS developed for routine care settings should take time constraints of outcome measurement into account. This is particularly relevant for patient-reported outcome measures (PROMs), which can be lengthy questionnaires, taking up considerable time of patients (PROM respondents) and health care professionals (PROM administrators and users). In real-world settings, patients might be less willing to complete lengthy questionnaires than when enrolled in trials where the purpose of data collection is clear, potentially leading to reduced response rates. For example, a COS developed for distal radius fractures recommended briefer measures for clinical practice than for research studies, as collecting lengthy questionnaires might not be possible in clinical practice, and clinicians require brief and simple indicators for clinical decision-making (48). The potential of smart devices for recording real-world and PROMs data is not yet broadly reflected in existing COS but may have a role to play in the future for reducing the burden of data collection.	+	++
Cost of data collection	Standardised data collection can require an investment in setting up an adequate infrastructure, including the procurement of appropriate instruments for outcomes measurement, as well the training of staff collecting and inputting data. Data collection standards should therefore be set with a view to the implementation of these standards and the resources required in a setting where research is not a priority. Some PROMs are in the public domain, while others require fees to be used. The scope of the COS to be developed and how it is implemented can inform whether license fees are an exclusion criterion.	++	++

TABLE 6 Feasibility considerations for selecting OMIs by importance to RW settings and PROMs (continued)

Consideration	Notes	Importance for: RW COS	Importance for: PROMs
Acceptability	Acceptability of the instrument for patients, questionnaire administrators and users of the information, factoring in feasibility and administration of the instrument (for which rates of missing data from previous studies can be informative), as well as content validity to ensure health care practitioners and researchers deem the information obtained with the instrument relevant (49,50). This extends to data collected from smart devices, including acceptability of automatic data generation (tracking) by patients, and the use of such information by health care practitioners and researchers.	+	++
Interpretability	Interpretability refers to several questions relevant for PROMs, including what scores of the instruments mean and how they are interpreted for clinical practice and research, as well as the interpretability of the findings from a specific study, which can be hindered by low response rates. Differently from laboratory measures, PROMs typically do not have cut-off values that constitute a meaningful improvement in health. In addition, COS developers might only be interested in subscales of existing instruments. However, without separate validation, scores of the subscale might not be interpretable (50).	o	++

Key: ++, highly relevant; +, relevant; o, not immediately relevant

CASE STUDY 4

Importance of using validated questionnaires

In a review of recommended PROMs in existing COS, DO→IT researchers found that a substantial minority (over one third) of instruments were single questions, rather than full questionnaires or subscales of existing questionnaires (see appendix C).

Using PROMs that are validated, as a single question or as a series of questions, is best practice.

The importance of first considering outcome domains before evaluating OMIs is particularly important for PROMS since there are many available. While specific questions might be required to assess some domains, other, more generic questions are likely to be included in existing instruments. For example, single item pain scales are often recommended although such scales are also part of larger questionnaires, such as the Short Form-36. In cases where COS recommend more than one PROM for different outcomes, a **mapping of individual items** in these instruments can avoid overlap in domains covered by one instrument. Recommending one PROM that covers more than one domain and/or outcome can reduce the burden on patients and staff.

TIMING

Provision of recommendations regarding timing and frequency of assessment with OMIs is essential. This may be particularly important in routine care settings where patients may present at ad hoc times.

SELECTION OF OUTCOME MEASUREMENT INSTRUMENTS

STAGE 5 KEY POINTS

- The process for identifying and selecting OMIs may be similar to selecting outcomes but with an additional assessment of measurement properties and feasibility.
- For COS that will be applied to RW settings, feasibility of administering instruments is particularly important.
- Mapping of PROMs may be helpful to check overlap in domains if a lot of PROMS are available that cover different domains.
- Both disease-specific and generic QoL tools are important to consider in a COS to generate the evidence needed by key decision-makers
- Consider and recommend important timing of OMIs, bearing in mind feasibility in RW settings.

WHEN NO OMI IS DEEMED AS HIGH QUALITY OR FEASIBLE

COS developers might find that available OMIs do not meet their desired criteria. For example, evidence on an instrument's validity might not be available in the target population of the COS or they may not cover the target domains (what to measure in Stage 3 and Stage 4). In a situation like this, possible ways forward include:

1. **Not recommending an OMI:** the problem of lack of an appropriate instrument is highlighted and development of such an instrument or validation of an existing instrument in the target population is emphasized as a future research priority (51).

2. **Recommending a 'placeholder' OMI:** while the lack of an appropriate instrument meeting all criteria is highlighted, an alternative measure is recommended to be used until a better instrument becomes available (49,52,53).

STAGE 6

IMPLEMENTATION AND UPTAKE

QUESTIONS TO CONSIDER

- What are some options to ensure COS are used after being developed?
- When should a COS be reviewed and updated?

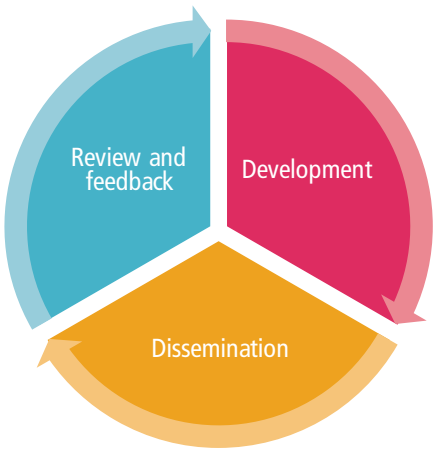
Dissemination:

awareness raising and or engagement and influence

- Conferences
- Peer review publication
- Press releases
- Methods guides
- Key organisations

Review and feedback

FIGURE 4
Implementation and uptake cycle



It is important to disseminate the COS widely and to engage with stakeholders, including those planning and undertaking research, key decision makers (regulatory and HTA bodies), clinicians and healthcare providers, and individuals with particular conditions. This section offers options to consider when promoting the implementation and uptake of a COS across the evidence pathway and within routine clinical care.

Figure 4 provides an overview of the development and implementation cycle of a COS with further details about each step provided below.

DEVELOPMENT

The rationale for the involvement of a broad range of stakeholders in the development of a COS has already been described in this toolkit (Stakeholder involvement). The stakeholders involved in the development of the COS can be considered 'future implementers'; they have a key role to play in their uptake and implementation, both in terms of future implementers of the outcome set themselves but also in disseminating the outcome set amongst their own networks and contacts (11).

DISSEMINATION

In order to maximise awareness, implementation and uptake of the COS, it is important that projects develop a **clear dissemination plan** early on. The plan should set out the target audiences, methods and responsible parties for dissemination (see example proforma in Table 7). Dissemination materials, for example, slide sets, commentaries etc. could be developed to support the different activities outlined in the plan. It is worth considering the preparation of a dissemination plan early in the development process.

TABLE 7 Example dissemination plan proforma

Purpose	Target audience	Method	Specific Activities	Timescales	Responsibility of:
Raising awareness about the existence of the COS	Researchers in the field	• Articles in journals • Presentations (oral/poster)	• [List Journals] • [List conferences]	March – June 2018	Members of the team with a research background

Projects should consider a range of options for disseminating a COS (8,11,54). This could involve simply **raising awareness** about the COS or **educating** about the use of the tools recommended within a COS, as well as **engaging and influencin**g a broad range of stakeholders from different organisations across the evidence pathway and from across different health care systems. Engagement activities should be targeted at those key organisations and individuals that are in a position to implement the COS within their own field of work and those who can help to increase demand for and use of the COS. Consideration should be given to those in the team that are best suited to leading each engagement activity. For example, team members from a research background may be better leading engagement activity with journal editors, whereas clinicians may be better leading engagement with other clinicians and healthcare providers. Options for dissemination are presented in Table 8.

TABLE 8 Dissemination options by aim or purpose

Awareness raising	• Publishing articles (see the Core Outcome Set–STAndards for Reporting [COS-STAR] Statement for a checklist of minimum reporting requirements for COS studies), editorials or commentaries in disease-specific journals and publications/websites aimed at relevant healthcare professionals. Articles could also cover use and utility of COS in finding meaningful insights (55). • Using existing project-specific dissemination channels e.g. websites, social media and newsletters. • Giving presentations at relevant conferences and meetings. • Listing the protocol and finalised outcome set in the COMET Initiative database (a searchable database of ongoing and completed COS) and highlighting it on the news feed of the COMET website. • Informing other organisations and initiatives focused on developing COS about the developed set e.g. ICHOM, OMERACT, CROWN etc. This stage could also be considered earlier in the process, for example during the development of the protocol. • Using prepared dissemination materials (such as slide sets, press releases etc.) with links to published articles, stakeholders involved in the development of the COS can raise awareness across their own organisations/networks and in their own countries.
Education	• It may be useful to develop guidance materials to facilitate dissemination such as training manuals on the OMIs and guidance on how interpretation of scores (including what a minimally important difference may be) (12).
Engagement and influence I Research	• Lobbying the pharmaceutical industry, through for example the European Federation of Pharmaceutical Industries and Associations (EFPIA), to encourage uptake of COS so that all companies are measuring the same outcomes. The EFPIA actively encourages the use of COS (56,57). • Lobbying Research Funders who are increasingly recognising the importance of COS. Funders can encourage the uptake of COS by making the selection of a COS (where available and appropriate) a specific review criteria. Some examples of trial funders that endorse the use of COS are given on the COMET Initiative website (56). • Prospective research registries (e.g. ISRCTN registry (who actively promote COS and use of the COMET database), ClinicalTrials.gov) provide an opportunity to engage with those undertaking research to inform and encourage them to use a COS as part of their research (37,58). • Journal editors could encourage authors to report the results for outcomes within COS in their submissions and embed COS in to the peer review process. • Systematic reviewers and guideline developers could be encouraged to use COS in their reviews/guidelines. Guideline developers could influence the uptake of COS through methods guidance and encouraging future researchers to use relevant COS (e.g. in its guidelines process and methods manual, NICE suggests that COS may be used where appropriate) (59).

TABLE 8 Dissemination options by aim or purpose (continued)

Engagement and influence II Key decision-makers and influencers	• HTA organisations, regulatory agencies and payers may use COS in their decision-making processes. They can influence researchers and manufacturers to use COS through guidance on HTA methods and scientific advice. • Patient advocacy and consumer groups can influence decision-making bodies to implement a COS and encourage healthcare systems to adopt COS for outcome and performance monitoring.
Engagement and influence III National and regional healthcare organisations	National and regional health systems and organisations collect and use data to monitor and evaluate performance and outcomes, and to drive improvements in health care quality. COS can support performance and outcome monitoring and evaluation and enable comparisons of health outcomes across providers and countries (60). This could include: • Aligning COS with national/regional performance monitoring frameworks through engagement with responsible bodies. • Aligning COS with national/regional healthcare minimum datasets. • Embedding minimum outcomes in to national/regional/local commissioning plans and contracts. • Engaging with clinicians and other healthcare providers to use COS as part of their routine practice.

REVIEW AND FEEDBACK

Periodic review and evaluation of a COS enables in understanding of any shortcomings and ensures it remains valid and relevant. A review provides an opportunity to assess whether implementation of the COS was successful and facilitates uptake (11).

The frequency of review depends on the disease context and speed of technological advances within that area. Project team members should be able to advise on the frequency that a COS should be updated based on their experiences. It is worth considering setting out planned reviews early in the development process.

The aim of the review should be to evaluate:

1. **How well the outcomes are being assessed and measured in research and/or clinical practice;**
2. **If there are any outcomes included in the COS that are no longer relevant or any new outcomes that should be considered for inclusion.**

Depending on resources and expertise within the project team, several options could be considered as part of a review (Box 2).

IMPLEMENTATION AND UPTAKE

STAGE 6 KEY POINTS

- The stakeholders involved in the developing a COS may be well-placed to assist with its implementation.
- The nature of dissemination may relate to raising awareness of a COS (i.e. using publications, presentations, press releases, social media) and to engaging with influencing researchers, key decision-makers, and national/regional healthcare organisations (i.e. lobbying).
- The reviewing frequency of a COS will depend on the disease context and speed of technological advances within that area.

BOX 2 Options for reviewing a COS

- Gaining feedback from key stakeholders who were involved in the development of the COS.
- Surveys/interviews/focus groups with stakeholders (e.g. target audiences set out in the dissemination plan).
- Using trial registries to assess the listed outcomes in planned, ongoing and recently completed trials and reviews (98).
- Systematic review of the literature to assess uptake of the outcome set in research and clinical practice (11).

QUESTIONS TO CONSIDER

- How can the preferences for outcomes that regulators/HTAs/payers require be captured within a COS?
- What mechanisms can be utilised to ensure patient perspectives on outcomes are incorporated within the COS?
- How should the industry perspective on outcome selection factor within the COS?

PERSPECTIVE AND REQUIREMENTS ON OUTCOMES FROM KEY DECISION-MAKERS IN HEALTHCARE

As noted earlier, COS developers should consider incorporating perspectives of a number of different stakeholders (see Stage 1).

This section addresses important considerations regarding a number of key stakeholders and makes suggestions for how their perspectives could be incorporated into a COS.

REGULATORY AND POST-REGULATORY DECISION-MAKERS[3]

The healthcare system and overall drug approval landscape in Europe is fragmented and different decision-makers (regulators, HTA agencies and payers) may have different preferences for outcomes. This can make it difficult to develop a COS that is applicable across Europe, much less internationally.

Appendices A and D provide a better understanding of the differences in roles across a selection of different decision-makers in Europe as well as the factors that may be influencing different outcome preferences (a brief summary is presented in Table 9). It is important to note that while the remit of the toolkit is focused on Europe, perspectives beyond Europe may also vary further.

3. These suggestions have been informed by exploratory research undertaken by DO→IT task 2.2.4 (see appendix D for more details).

TABLE 9 Summary of findings from exploratory research on outcomes preferred by European regulators and HTA agencies

OUTCOMES	Regulator	HTA
EFFICACY (Regulatory) / EFFECTIVENESS (HTA)		
Clinical endpoints	Trial endpoints Detailed guidance in different disease areas	Longer-term final outcomes (i.e. overall survival) often requiring modelling Acceptability determined case-by-case
Patient-reported	Accepted if validated, but not usually primary endpoint Disease-specific QoL instruments preferred (validated) Detailed guidance available	Most accept validated PROs All accept and some require QoL Some prefer disease-specific QoL instruments, others generic QoL instruments Acceptability of QoL instrument case-by-case (no stated preference)
Surrogate	Term 'surrogate' not used All outcomes if demonstrate a clinically relevant response (guidance on PFS in cancer).	All accept (if validated) but some more open Acceptability determined case-by-case Few have guidance about validation requirements
SAFETY		
Safety	All safety outcomes/concerns, includes early or exploratory concerns Detailed guidance in different disease areas.	All require some safety Range of requirements No clear differences between agencies

Payers

As regulatory and HTA perspectives on outcomes differ, both perspectives should be obtained when developing a COS. Payers preferences are likely to be similar to HTA agencies so it may not be necessary to specifically obtain payer perspectives for the COS.

HTA agencies

Obtaining an HTA view is complicated as the landscape and some outcome preferences differ between agencies across Europe (appendices A and D). COS developers should consider how best to obtain a varied and representative perspective for their COS, ensuring as wide a range of perspectives as possible, depending on the scope for the COS. For example, a number of HTA agencies may need to be selected to ensure a representative view across differing perspectives. Some suggestions for how to determine HTA perspectives are provided in Box 3 and a case study of experiences with HARMONY is found in Case study 5.

BOX 3 Incorporating HTA preferences and views of outcomes in COS

- Choose which HTA agencies to elicit views; range of HTA agencies can provide a broader HTA perspective, taking into consideration different policies, methods and remits.
- Consider outcomes in previous HTA assessments for other products in the same disease area and acceptability of these outcomes.
- Check existing scopes in the disease area for HTA agencies that produce them to understand pre-specification preferences on outcomes.
- Consider involving HTA agencies within the formal consensus group to agree outcomes and measurement instruments (Stage 4).

(Note: a 2017 EUnetHTA JA3 report includes a comprehensive list of HTA agencies in Europe (36). Annex 1, Table 3 of this report notes which agencies conduct scopes. However, it is important to note that while some agencies develop scopes, this does not necessarily mean that outcomes are pre-specified in this scope. To our knowledge this information has not be summarised in a publicly available form. The exploratory research in appendix D has summarised this for a selection of European regulatory, HTA and payer organisations.)

CASE STUDY 5 Identification of HTA perspectives on outcomes in haematological malignancies – experience from HARMONY

For part of the HTA input into identifying preferences for outcomes within the HARMONY project, an audit of publically available, key selected HTA reports (including scopes where applicable, HTA evaluations and product submissions) for products for the following 7 different types of haematological malignancies: multiple myeloma (MM), acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphomas (NHL), myelodysplastic syndromes (MDS) was undertaken.

The analyst and consideration of previous scoping preferences and outcome prevision by product sponsors within a disease could provide a timely and resource light mechanism for HTA input into COS development.

www.harmony-alliance.eu

Regulators

It is less important to obtain a varied European regulatory perspective as there is little variation in outcomes preferences since European legislation covers all authorisation procedures for marketing authorisation and pharmacovigilance (61). Suggestions for determining regulatory perspectives are provided in Box 4.

BOX 4 Incorporating regulatory preferences and views of outcomes in COS

- Check detailed EMA guidance in the disease area for regulator preferences regarding outcomes (35).
- Review European public assessment reports (EPAR) in the same disease area, considering acceptability of outcomes (34).
- Consider EMA qualification of novel methodologies procedure which enables advice on methods not covered in available guidance (i.e. validation of a biomarker, validation of a PRO tool) (99). This procedure could be also be used for validating/implementing a COS (250-day procedure).
- Consider utilising the EMA Innovation Task Force, a forum for early dialogue to support the development of innovative methodologies by fostering greater collaboration across the regulatory network and with academia. This procedure could be used for validating/implementing a COS (100).
- Consider involving a regulator within the formal consensus group to agree outcomes and measurement instruments (see Stage 4).

PATIENTS

Patient participation in COS development studies has been defined as taking part in a study alongside clinicians and other stakeholders in a consensus process, while **patient and public involvement** has been defined as more active involvement in the design and oversight of a COS study (14,32).

As COS development often takes place over time with different activities; patients can provide input to COS studies as participants or research partners during any of these stages (10). Qualitative research can be useful to gain patient perspectives on aspects of their condition and experience that may be very useful for developing COS including the signs that a treatment is working and, thus, identify important outcomes (14) (Stage 3). Whereas including patients in a consensus process can ensure a wide population is involved in selecting outcomes for a COS (see Stage 4).

A lay summary of what a core outcome sets which could be useful to share with patient participants can be found at www.comet-initiative.org/assets/downloads/COMET Plain Language Summary v4.pdf (101).

Patient recruitment for the COS development: practical considerations

Patient views can be obtained from the patients themselves or carers, patient advocates, patient organisations, or patient experts (15). The type of input will depend on the purpose. For example, patient or carer organisations or patient experts may better understand technical language and the overall research process so could be involved in setting the aims and design of the study. However, individual patients or carers can contribute from their subjective experience – their input may be best provided through qualitative research to identify outcomes (Stage 3) or as participants of a consensus process (Stage 4).

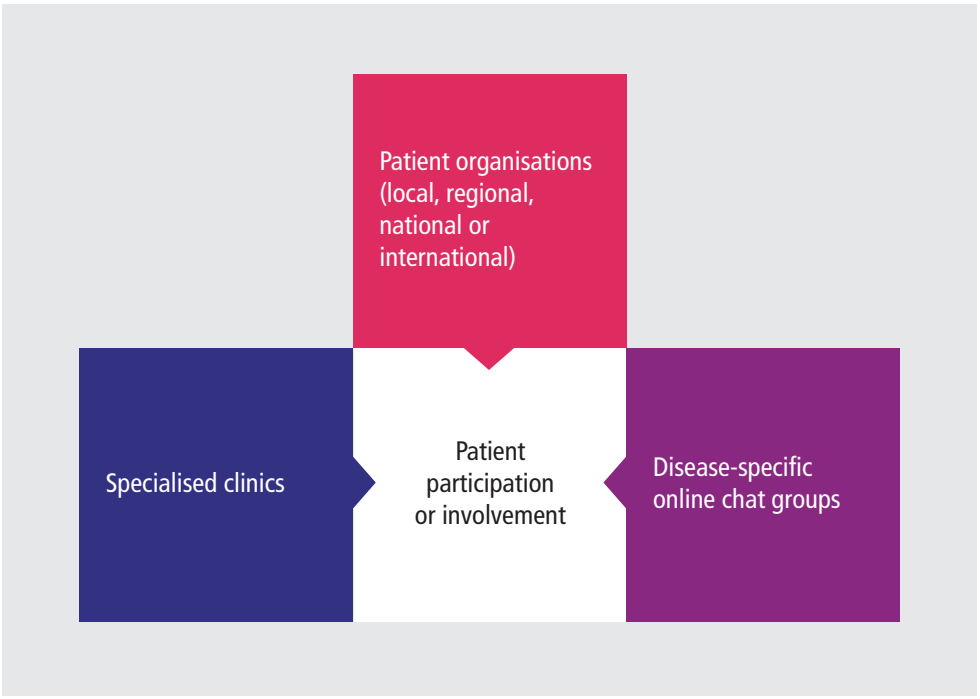
The COMET handbook recommends including as many patients or patient representatives as possible in the consensus process (11). The People and Patient Participation, Involvement and Engagement (PoPPIE) Working Group recommends that patients are chosen according to their abilities and interest to either participate or be involved in a COS study. A range of sources could be considered, depending on the needs of the disease area.

Some resources for identification of patients being potentially interested and suitable for either involvement or participation in a COS development process are included in Figure 6.

Additional considerations in involving patients include maintaining patient input over time and facilitating patient input (appendix E).

Appendices A and D include an overview of factors influencing patients' and the public's decisions to share their data.

FIGURE 5 Potential sources to obtain patient views



INDUSTRY

In order to drive efficiency and ensure effective healthcare systems, industry recognises that standardised health outcomes and COS are needed to improve patient care through more patient-centred data. In line with these objectives, a Strategic Alliance Partnership between ICHOM and EFPIA was recently announced, demonstrating the importance of stakeholder collaboration and exchange as an important driver (57).

Some ways to incorporate industry perspectives into a COS were covered earlier (Stakeholder involvement).

COS use and the pharmaceutical industry

The industry is a key stakeholder for generating evidence, either through randomised controlled trials or post-approval Real World Evidence (RWE) studies. There is an increasing need to generate patient-relevant evidence once a product is accessible for a broader patient population. RWE as a cross functional discipline of scientific experts reflects a key area for COS development, adaptation and application, such as for bridging the efficacy-effectiveness gap between clinical settings and routine care. A more detailed summary of the industry perspective on the journey of RWE, including several aspects of generating evidence can be found in appendix F.

The basis for evidence generation is a plan that summarises all relevant research questions and study plans, including definition of patient populations, treatment comparisons, identification of data sources and outcomes definitions. It is highly relevant for the industry to develop **consistent definitions** across multiple research activities to ensure transparency, reproducibility and credibility of findings. COS could help and enable the industry to engage with other relevant stakeholders to define patient relevant outcomes that matter for the patients as well as to ensure consistency within and across research collaborations. Industry could be included in developing COS.

Implications of COS: application of COS within industry

In the near future, more industry stakeholders might play a role in using, adapting and developing COS, including promoting the use of new technologies, wearables and sensors as ways to collect outcomes. COS can be seen as an enabling tool for new business models in the industry, creating consistent definitions in outcomes-focused and value-based models with positive implications on patients, clinicians, providers, industry and payers. Automated rapid cycle analytics might use COS to further drive efficiency in analytics and evidence generation.

In the more distant future, bigger datasets, new data sources, linked data systems, next generation data and more complex databases are likely to emerge. COS can help in the development of new EHR and data capture systems through the use of consistent sets of outcomes. This is more efficient for the database creator and may support outcomes-focused healthcare systems. These opportunities could be achieved through partnerships and strategic alliances (such as EFPIA and ICHOM) between industry and relevant healthcare institutions. Ideally, collaboration and partnerships should catalyse the process and contribute to improving overall patient care.

QUESTIONS TO CONSIDER

- Is there additional data that should be collected alongside the COS to contextualise the outcomes?
- What types of data could be included as part of a minimum data set?
- How can a minimum data set be determined?

IMPORTANT DATA OTHER THAN OUTCOMES

In addition to COS, there will be **additional data** which should be collected as part of a minimum data set to contextualise the outcomes collected in the COS.

This additional data may include **contextual factors** that interact with the effect of a medicine.

As with methods for developing a COS, there is no gold standard method for developing a minimum data set. Minimum data sets could be determined alongside, or subsequent to, developing the COS. ICHOM include the use of this additional data in their 'standard sets'. Unfortunately, many of the COS initiatives to date have omitted this area, which can result in the limited usability of the outcomes collected as they cannot be contextualised and fully utilised by key decision makers.

Contextual factors that interact with the effect of a medicines have been referred to as drivers of effectiveness, effect modifiers, or confounders. See Table 10 for examples of different types of contextual factors.

BOX 5 Data on contextual factors is important for:

- Sub-group analysis
- Enabling exploration of which data are drivers of effectiveness/confounders/ effect modifiers
- Adjusting for selection bias.

IMPORTANCE OF COLLECTING DATA ON CONTEXTUAL FACTORS

Collecting contextual data can enable further analysis of outcomes but it is also useful for certain decision-makers (such as HTA agencies or payer) to determine the applicability of the results to different populations. While it is important for trials, it is particularly so for outcomes collected in RW settings as they are particularly at risk of confounding bias. This availability of data on potential confounders can enable researchers to investigate and adjust for these confounders (62). Acknowledgement, examination of and adjustment, where possible, of these confounders is necessary to enable decision makers to better understand the uncertainty with the estimates of treatment effect and, therefore, make more informed decisions. A summary of methods that could be used to adjust for bias are found in Faria R et al (2015) (62).

TABLE 9 Categories of contextual factors and examples

Category[1]	Examples
Related to use of the medicine	Dosage regimen, administration route
Related to the patient[2]	Demographic data (e.g. age, gender, ethnicity) Lifestyle factors/health behaviours (e.g. smoking status, alcohol consumption, physical activity) Comorbidities (see Glossary) Family history (e.g. of the disease or risk factors) Other prognostic or risk factors[3] including biomarkers (see Glossary)
Related to the disease	Stage of disease
Related to the healthcare system	Coverage, resource use and cost[4] Caregiver information (where applicable) Healthcare resource utilisation (e.g. hospital use)

1. Categories of contextual factors taken from IMI GetReal (63).

2. Some factors may help validate surrogate outcomes included in the COS.

3. Including data on risk factors for developing a disease may be useful, depending on the scope of the COS. For example, those interested in identifying people with Alzheimer's disease before they are symptomatic may wish to collect information on risk factors such as biomarkers which may predispose someone to developing Alzheimer's disease (i.e. age, genetic causes, medical history and lifestyle) (NICE guideline) (64).

4. This could also be part of the COS – collecting this data is essential for HTA agencies and payers.

DEVELOPING A MINIMUM DATA SET

Projects should take a systematic approach to identifying the data to include as part of a minimum data set. The steps outlined below provide some options for projects to consider when developing a data set. The aims of the research, such as whether the study is to establish causality, comparative effectiveness or to validate surrogates, may inform what data is prioritised.

Considering the content of the project team

Projects could use the same project team established to develop the COS (see Stage 1). Additionally, input from epidemiologists, statisticians, and registry or database managers could advise on what data is available and what is already collected and used.

Collecting current knowledge on contextual factors

As with developing COS, any minimum data set already in use for a health condition in question should be examined and checked whether it is useable.

A systematic review of prognostic studies (and risk factors, depending on the scope of the work) within a disease area would be advantageous, although resource intensive. The MRC PROGnosis RESearch Strategy Partnership (Progress Partnership) project has created some useful resources related to

prognostic research (65). Advice on conducting literature reviews to explore drivers of effectiveness is available from the RWE Navigator, developed by the IMI GetReal project (66).

Options for identifying outcomes in Stage 3 could be used to determine current knowledge on contextual factors such as:

- identifying existing reviews or minimum data sets;
- conducting a systematic review;
- conducting qualitative research (such as interviews or focus groups). Individual interviews with experts can also be used to explore the potential effect modifiers/confounders /drivers of effectiveness (for more information about IMI GetReal work on this see here (67));
- examining other sources of data such as patient registries and electronic health records.

Selecting the minimum data set

There is no agreed methodology on selection and agreement of a minimum data set. Consensus methods as described in Stage 4 could be considered; however, these are resource intensive. The minimum data set could be developed alongside developing the COS, though it will be important to ensure that the work is distinguished. Alternatively, a more informal discussion could be used to agree minimum data sets.

When agreeing a minimum data set it is important to be pragmatic about what data is **feasible** to collect and what data will actually be **useful**. This is particularly important in routine care settings. Enough relevant data should be collected to enable the data to be used, whilst making sure that it is not too much of a burden to the data subject and data collector. Data sets should also comply with **legal** and **data governance frameworks** concerning the usage and sharing of data. For example, data security, data privacy, and appropriate anonymisation or pseudonymisation of data according to General Data Protection Regulation (GDPR) EU data protection rules as of May 25, 2018 (68).

EXAMPLE Minimum data set recommended as part of Heart Failure Data Collection Reference Guide by ICHOM (102)

ICHOM Standard Sets include baseline conditions and risk factors to enable meaningful case-mix adjustment globally, ensuring that comparisons of outcomes will take into account the differences in patient populations across not just providers, but also countries and regions.

Health behaviours
- Smoking status
- Alcohol use

Demographic factors
- Sex
- Ethnicity
- Age

Comorbidities and baseline health status
- Hypertension
- Diabetes
- Renal dysfunction
- Prior MI
- Atrial fibrillation
- Chronic lung disease
- Body mass index
- Ejection fraction
- Diagnostic categories

GLOSSARY

Adverse event	Any undesirable event during or after the use of a medicine or other intervention but is not necessarily caused by it. However, an 'adverse effect' (or 'adverse drug reaction' when used with medicines) is an unintended effect that is harmful or unwanted and suspected to be related to or caused by a medicine or other intervention.
Big data	Big data in health refers to largely routinely or automatically collected datasets, which are electronically captured and stored. It is reusable in the sense of multipurpose data and compromises the fusion and connection of existing databases for the purpose of improving health and health system performance. It does not refer to data collected for a specific study (69). Disease or product registries may be considered as big data.
Biomarker	measurable characteristics that provide an indication of normal biological or pathogenic processes, or responses to an exposure or intervention. There are different types of biomarkers that could be measured, including those that: (1) identify risk factors for a disease, (2) detect or confirm the presence of a disease or (3) indicate disease progression in individuals with a disease (70,71).
Comorbidities	Other diseases or conditions that a person has in addition to the disease or condition being treated or studied (HTAi definition) (72).
Composite outcome	Combines two or more of single events (e.g. mortality, non-fatal myocardial infarction, stroke, hospitalisation and revascularisation procedures) in one endpoint showing the overall and clinically relevant treatment effect. A composite endpoint usually refers to combined morbidity and mortality endpoints; it may also be a combination of patient-reported, observer reported or clinician reported measures (EUnetHTA) (2). Quality of life is a commonly used composite outcome.
Confounder	A confounder is a factor that is common to the cause and the outcome of interest (such as smoking while drinking). The confounder may hide an actual relationship between cause and outcome or falsely suggest a relationship that does not really exist (HTAi definition) (72).
Confounding bias	"Systematic error that occurs when the estimate of a measure of association between exposure (e.g. healthcare intervention) and outcome (e.g. health status) is distorted by the effect of one or several extraneous variables (confounding factor(s)) that are independently related to the exposure and outcome." (IMI GetReal) (73,74).
Confounder	"A factor that is associated with both an intervention (or exposure) and the outcome of interest" (Cochrane) (75).
Contextual factor	"Variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers" (13).

GLOSSARY

Core outcome set (COS)	The minimum set of outcomes that should be measured and reported in a specific condition and in a particular setting, which may include clinical trials, research more generally, and routine care (COMET initiative) (18).
Domains	"distinct elements of a disease and can usually be measured by many different instruments and /or scales, such as function, pain, cost, safety and quality of life (HOME)" (76).
Drivers of effectiveness	Contextual factors that interact with the medicine's pharmacological effect in the real world; if they not properly accounted for, they may have an impact on the effect of the medicine reported in trial (IMI GetReal) (73,74).
Economic evaluation	Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences (Drummond 2005) (77).
Effectiveness	"The extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice. (See also 'ideal vs. usual conditions') (High Level Pharmaceutical Forum, 2008)" (IMI GetReal) (73,74).
Effect modification	"Occurs when the magnitude of the effect of the primary exposure on an outcome (i.e., the association) differs depending on the level of a third variable. (Adapted from VanderWeele, 2009)" (IMI GetReal) (73,74).
Effect modifiers	Variable that leads to effect modification (see above).
Endpoint	Typically refers to the event or outcome measured and reported in a trial.
Health-related quality of life (HRQL or HRQoL)	Specific type of patient-reported outcome; a broad concept which can be defined as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being. The notion of multidimensionality is a key component of the definition of HRQL (EMA) (78).
Health technology assessment (HTA)	The systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision-making regarding health technologies (HTAi definition) (72). It usually involves multiple disciplines and includes the summarising of information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.

Intermediate outcome	A type of surrogate outcome related to the timing of the outcome. An intermediate outcome is one that is reported before the timing of interest; mathematical modelling is sometimes used using the intermediate outcome to predict the outcome at the desired time point.
Managed entry agreements	An approach to reimbursement which involves 'an arrangement between a manufacturer and payer/provider that enables access to (coverage or reimbursement of) a health technology subject to specified conditions' (79).
Minimum dataset	All data that should be collected on a condition, including both outcomes in the COS, as well as additional contextual data (referred to as a Standard Set by ICHOM (19)).
Outcome	A test or treatment's impact on health or wellbeing. (HTAi) (72). Clinical outcomes should be clinically and patient-relevant, and may also be patient-reported (EUnetHTA 2013) (2). Some organisations refer to clinical outcomes as clinical endpoints. A clinical outcome could be reported on behalf of the patient (see definition of PRO below).
Outcome measure	Typically refers to the instrument or tool used to collect outcome data. It is sometimes used to refer to the outcome itself.
Outcome measurement instrument (OMI)	An instrument or tool used to collect outcome data.
Patient-reported outcome (PRO)	Any outcome evaluated directly by the patient and based on patient's perception of a disease and its treatment(s). PROs and quality of life (QoL) are often referred to interchangeably; it is true that quality of life reports are typically generated by the patient, but a PRO is an umbrella term for any outcome that is reported by a patient. Patient reported outcome is an umbrella term covering both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc (EMA) (78). A PRO is measured using a patient-reported outcome measure (PROM).
Patient-reported outcome measure (PROM)	Instruments that are used to measure patient-reported outcomes, which are defined as direct reports about a patient's health and function without health care professionals, carers or relatives interpreting the patient's own record (50).
Patient-relevant or patient-focused outcome	An outcome that has been identified as meaningful by patients. It is often incorrectly inferred that PROs are patient-relevant outcomes. A PRO may not necessarily be an outcome that is most relevant to a patient; it may be more of interest to clinicians such as adherence to a treatment. Similarly a patient-relevant outcome may not be a PRO e.g. mortality.

GLOSSARY

Prognostic factor	" 'Prognostic' factors are those which, in people who have the condition, influence the outcome (like resectability of tumour for lung cancer, duration of intubation for CLD, or an unhealthy joint interest in home furnishings for staying in love)." (80).
Real-world data	"An umbrella term for data regarding the effects of health interventions… that are not collected in the context of highly-controlled RCTs…it can be either primary research data or secondary research data derived from routinely collected data…RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases"(IMI GetReal) (73,74).
Real-world evidence	"Evidence derived from the analysis and/or synthesis of real-world data (RWD)" (IMI GetReal) (73,74).
Real-world setting	Settings in which RWD is collected.
Resource use	Refers to both costs of treatment and other related costs associated with delivering the treatment such as staff time.
Risk factor	Any attribute, characteristic or exposure that increases the likelihood of an individual developing a disease (Cochrane) (75,81). Some may consider risk factors to be factors that impact on disease progression but these factors are typically considered to be prognostic factors (71,80).
Safety	Safety tends to refer 'to serious adverse effects such as those that threaten life, require or prolong hospitalization, result in permanent disability, or cause birth defects. Indirect adverse effects, such as traffic accidents, violence, and damaging consequences of mood change, can also be serious' (Cochrane) (75).
Selection bias	Bias that arises when comparing the effect of a treatment in groups that are systematically different on variables that have an independent effect on the outcome on interest (62).
Side effect	Any extra effects from a drug, treatment or procedure that are not planned, even when used as instructed. They do not necessarily cause harm (HTAi) (72).
Surrogate outcomes	Outcomes measured in the short–term that predict longer–term patient–focused outcomes. For example, reducing blood pressure reduces the likelihood of death (HTAi) (72).
Standard set	The term used by ICHOM to refer to its standard sets of outcomes. Unlike a COS, it also includes outcomes, case-mix variables, measurement tools, data sources and time points for data collection (ICHOM) (19)

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APPENDICES AND PUBLICATIONS

Appendix A. Supplementary information on stages for developing COS and the 'Evidence for all section.

The following appendices include original work and case studies informing the toolkit. These can be found at http://bd4bo.eu/index.php/toolkit.

Appendix B. Identification and selection of core sets of outcomes and their application to real world settings: a targeted review based on the COMET database: Report from IMI2 DO→IT working group for Task 2.2.1.

Appendix C. Patient-reported outcome measures in core outcome sets. Report from IMI2 DO→IT working group for Task 2.2.2.

Appendix D. Outcome preferences across selected European regulators, HTA agencies and payers. Report from IMI2 DO→IT Task 2.2.4.

Appendix E. Patient perspective and expectations on the use of real-world outcomes. Report from IMI2 DO→IT Task 2.2.5.

Appendix F. Industry perspective and expectations on the use of real-world outcomes. Report from IMI2 DO→IT Task 2.2.6.