



# Big Data for Better Outcomes

## **Appendix A: Supplementary detail for toolkit stages and section on 'Evidence for all'**

## Stage 1. Scoping

### **Stakeholders**

An international Delphi survey among experienced COS developers and users found agreement to include the following stakeholder groups in COS development: 1) those using the research (including clinical researchers and industry), 2) healthcare professionals (providing expertise for the condition in question), and 3) patients with the condition or their representatives (1). While this exercise did not reach consensus on the inclusion of regulators and HTA bodies, the trajectory of COS suggests that their inclusion will be crucial in the future to ensure that COS can be used across the evidence development programme.

### ***Link to key glossaries for definitions of key terms***

[Health Technology Assessment International \(HTAi\)](#)  
[IMI GetReal Project](#)  
[Cochrane](#)  
[EMA](#)

## Setting for COS

### *Case study 1: Scope of COS for cardiovascular disease (CVD), Alzheimer's disease (AD), haematological malignancies (HM) and prostate cancer (PC)*

COS that have been developed for the health conditions currently being researched by BD4BO projects were reviewed by DO>IT researchers (see Appendix B). There is variation in the reporting of aspects of the scope of the COS. All report the setting of the COS as well as the health condition it pertains to. Approximately half of the COS developed for CVD, AD and HM described the clinical characteristics of those the COS targeted, however the majority (12 out of 13) did so in the area of prostate cancer. Few studies reviewed did not specify the intervention; one in CVD, two in AD and three in HM. However, each of these may have been considered when developing the COS but not reported on.

*Table 1. Reporting scope of COS in CVD, AD, HM and PC*

	CVD	AD	HM	PC
<b>N</b>	<b>7</b>	<b>5</b>	<b>7</b>	<b>13</b>
<b>Setting</b>				
Recommended outcome measures/ recommendations made	0	2	1	4
Clinical trials	0	0	1	0
Practice	1	2	0	2
Clinical research	0	0	0	0
Clinical research and practice	0	0	2	0
Clinical trials and clinical practice	6	0	0	0
Clinical trials and general practice	0	0	1	0
Clinical trials or clinical research	0	2	2	8
COS PRO	0	0	0	1
<b>Health condition</b>				
Defined health condition	7	5	7	13
<b>Target population</b>				
Population characteristics described	0	0	0	3
Clinical characteristics described	4	3	4	12
<b>Intervention</b>				
Not specified	1	2	3	0
Any	3	1	4	6
All intervention types	0	0	0	1
Drug treatments	1	0	0	1
Surgery	1	0	0	0
Disease modification	0	1	0	0
Psychological & behavioural	0	1	0	0
Mechanical	1	0	0	0
Focal/salvage ablative therapy	0	0	0	2
Radical prostatectomy, radiation therapy, and surveillance (as treatment alternatives)	0	0	0	1
Active surveillance, watchful waiting, radical prostatectomy, external-beam radiation therapy, brachytherapy, androgen-deprivation therapy (ADT), focal therapy, other methods.	0	0	0	1

## **Stage 2. Use of available COS**

No supplementary information.

## **Stage 3. Identification of outcomes**

No supplementary information.

## **Stage 4. Methodology for COS selection**

No supplementary information.

## **Stage 5. Selection of outcome measurement instruments (OMIs)**

### ***Importance of conducting the ‘what’ and the ‘how’ separately***

The definition of OMI (the instrument or tool used to collect outcome data) is important from a methodological point of view, as it highlights the difference between *what* to measure (the outcome) and *how* to measure it (the OMI). Keeping the two stages separate from each other forces researchers to take a systematic approach to COS development and allows them to keep an open view on potentially important outcomes and ways to measure them. By using the opposite approach (i.e. deciding *what* to measure and *how* to measure at the same time), it is likely that COS developers would restrict their deliberations to what they already know about the recommended outcomes and the available instruments in a specific disease area. For example, consider a situation where COS developers discuss possible instruments to measure pain in patients with rheumatoid arthritis; without having first separately discussed the domain (*what* to measure), some COS developers might understand this more broadly as relating to the impact of pain on overall health-related quality of life or well-being, and some more specifically as relating to an assessment of pain itself. They are therefore likely to propose very different OMIs, such as the Short Form-36 for overall health-related quality of life, and a pain visual analogue scale for pain assessment. By separating the two stages, the COS developers might find that they are interested both in current pain levels but also in the functional impact of pain, as two separate domains. Having defined these domains, they can now search for relevant OMIs to capture these domains and take a systematic approach to selecting these based on pre-specified criteria.

### ***Further text related to selecting OMIs in real-world settings***

The promise of the ‘big data revolution’ is based to a large extent on the potential value of reusing existing data in health care, in particular from routine data sources, such as insurance claims data, electronic health records, and primary and secondary care data bases. Researchers that aim to use existing data sets to benefit from large volumes of data (rather than solely relying on prospective data collection) need to be aware of additional considerations to take into account when agreeing on outcome measures to use.

First, generic routine data bases, such as primary care records or insurance claims databases may not contain disease-specific outcome measures, such as tender joint counts or cognitive assessments. These data sets might be better equipped to study research areas with more generic outcomes, including hospitalisations, use of prescription drugs, and laboratory measures.

Second, patient-reported outcome measures may not be included in routine data bases. In a mapping exercise of target domains recommended in COS in Alzheimer's disease, DO-IT researchers found that information on activities of daily living/function was available in 25 out of 47 datasets included in the EMIF platform, and instruments targeting overall quality of health in only 11 out of 47 datasets. COS developers who aim to include retrospective analysis of routine data in the scope of their COS should therefore consider the availability of specific in these data sets when selecting recommended PROMs.

Finally, the reliability of the outcome measure chosen should be assessed in the light of its routine measurement. Reproducibility of findings from routine data sources is an important concern, and potential problems with the reliability of data from routine data sources have been documented in the literature. For example, pilot projects for the use of electronic health data for post-market surveillance of new medicines showed that detection of safety events can vary widely due to a number of factors, including which routine data set is used (2). A review of 33 electronic health record studies in acute myocardial infarction revealed that the vast majority relied on diagnosis codes, rather than using electrocardiogram or biomarkers as outcome measures (3). When cross-referencing the cases identified through electronic health records algorithms used in these 33 studies with other means of outcome ascertainment (such as manual chart review), the positive predictive value of data extracted from electronic health records ranged from 20% to 100%. This demonstrates the need to carefully consider whether selected outcome measures are available in the routine data bases proposed for the research project and ready to be used, and to review the validity of the data source with respect to the selected outcome measure (4).

The fragmented landscape of PROMs, with a wealth of instruments that are often developed ad hoc and without considerations of available alternatives potentially covering similar domains, is well documented in the literature, but this evidence now shows that a wide variation of PROMs also exists in the context of agreed minimum standards for research. In COS of high methodological quality, the recommendation of a number of different instruments can be the outcome of a structured process with distinct deliberations guiding the selection of specific instruments that are needed for measuring different domains. However, our review indicates that recommended PROMs can have item overlap that is not necessarily considered by PROM developers and therefore suggest that there is scope for COS developers to more carefully consider available instruments and their contents before selecting one as a recommended measure.

### ***PROMs in the context of COS and possible item overlap***

A team of DO-IT researchers conducted a review of all COS in the COMET database that recommended PROMs as instruments (see appendix C for details). In a total of 72 COS development studies, a heterogeneous landscape of recommended PROMs was revealed. Out of a total of 310 unique instruments recommended in these 72 COS development studies, 92% were recommended in only one COS. The only two instruments recommended in more than three COS were the Short Form-36 and EQ5D-3L questionnaires.

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The wealth of existing PROMs makes it particularly important to first specify which patient-reported outcome domains should be measured, and then systematically evaluate available instruments for their content before selecting a recommended PROM. In the review of recommended PROMs in COS, a substantial minority (over one third) of instruments were single questions, rather than full questionnaires or subscales of existing questionnaires. While specific questions might be required to assess some specific domains, other, more generic ones 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, a mapping of individual items in these instruments can avoid overlap in domains covered and reduce the burden on patients filling out all recommended questionnaires and staff administering them.

An example of a systematic approach to gaining an overview of available PROMs and their contents, and making an informed decision on what domains are essential for inclusion exists for oesophageal cancer. Macefield et al. propose the following steps to identify which patient-reported outcome domains should be included in a core outcome set:

- 1) Identify validated PROMs used in the disease area through a systematic search
- 2) Obtain copies of these PROMs
- 3) Extract scales and items from the PROMs and examine for similarity
- 4) Categorise the items into conceptual health domains and proceed with selection of relevant domains (5).

### ***Criteria for PROM selection***

COS developers have used a wide range of arguments to support their choice of recommended PROMs. In some cases, the authors relied on the principle of 'standard practice' being the instrument commonly adopted in clinical studies of a specific condition. In some others, the PROM was recommended in the absence of superior tools. There appears to be scope for new COS developers to follow methodological recommendations about assessing the measurement properties of available instruments (such as the COSMIN guidelines presented above) more closely than previous researchers. Only few existing COS development studies made reference to some forms of validation and/or reliability, although no definition for this was given in most cases; whenever further details were provided, 'reliability' was described as 'internal consistency', 'discrimination' or 'test-retest'; for 'validity' (or 'truth') a distinction between several types was made (i.e. 'concurrent/convergent validity', 'divergent validity', 'discriminant validity', 'content validity') (6–8).

Another criterion to consider for the selection of PROMs can include interpretability. This includes several questions, including what do 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 (9).

Finally, acceptability of the instrument for patients, questionnaire administrators and users of the information can be considered (9,10). This criterion factors in feasibility and administration of the questionnaire (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.

- **Time taken** to answer the questionnaire: lengthy questionnaires can put a burden on patients which might lead to reduced response rates. In real-world settings in particular, patients might be less willing to complete lengthy questionnaires than when enrolled in trials where the purpose of data collection is clear.
- **Administration mode:** questionnaires can be administered paper-based, over the phone, via computer or smart devices. Flexibility in how the instrument can be administered may be desired, but validity of different administration modes needs to be established. In real-world settings, the burden of data collection on the administrator should be taken into account, as dedicated staff are unlikely to be available.
- **Standardised administration:** Novel approaches to patient-centred electronic health portals may enable additional collection of patient-reported outcomes data. However, to reduce measurement error, standardised administration of the questionnaire is desirable and includes considerations of instructions for the instrument to be completed, such as specific time for filling out the questionnaire, maximum time allowed, and number and type of reminders sent to patients.
- **Cost considerations:** 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.
- **For international use:** consideration should also be given to the availability of validated translations of the questionnaire, which take into account language and local contextual factors.

### **Methods specific to PROM selection in existing COS**

A review of all COS included in the COMET database that included a recommendation on PROM as instrument showed that only few authors provided details on specific methods in selecting PROMs. An OMERACT group reported that PROMs were discussed separately from other outcomes included in the COS by organizing a dedicated break-out session attended by patient research partners, in addition to researchers and clinicians, a group composition that differed from those of other break-out sessions which did not involve patients (11).



Overall, no notable differences could be detected with respect to the methodological approach to PROM selection vs. selection of other instruments. Among the available techniques for generating consensus on PROM selection, the Delphi technique by using mailed or online surveys was reported in some cases (12–14); in another study, Delphi was used for gaining consensus from healthcare professionals, while patients were separately involved in a focus group (15).

## **Stage 6. Implementation & uptake**

No supplementary information.

### **Evidence for all**

The work to complete the following sections related to regulators, HTA agencies and payers was drawn from exploratory research conducted with a selection of European regulatory, HTA and payer organisations. The overall aim was to better understand the processes and policies of these stakeholders and consider how these may influence the types of outcomes preferred by these organisations. The research included web-based searches for guidance documents and semi-structured telephone interviews to gather tacit knowledge not covered within the publicly available information (more information about the methods and results from this work is found in appendix D).

### **Regulators**

#### **Background**

The role of a regulator is to facilitate development and access to medicines, evaluate applications for marketing authorisation, monitor the safety of medicines across their lifecycle, and provide information on medicines to healthcare professionals and patients (16).

The system for regulating medicines in Europe is based on a closely-coordinated regulatory network of 33 national authorities in the Member States of the European Economic Area (EEA) working together with the European Medicines Agency (EMA) and the European Commission (16). Regulators conduct a benefit-risk assessment of medicines. They are interested in effect of a drug in trial settings and/or in clinical practice; the definition of efficacy used by regulators includes both these settings.

European legislation covers all authorisation procedures for marketing authorisation and pharmacovigilance (17). As a result, the process and methods used by European regulators are broadly the same.

#### **Preferred outcomes**

In the regulatory world, the term endpoints (see glossary in main toolkit document) is used more frequently than outcomes. As a result of the European legislation, there are few differences between European national regulators in terms of what outcomes they require in order to make decisions. The EMA has published detailed guidance about preferred outcomes, and any preferred instruments for measuring these outcomes, across different disease areas; this guidance is also followed by national regulators (18).

The main types of outcomes of interest to national regulators include safety and efficacy. Outcomes must be clinically- and patient-relevant. In the recently published addendum to the ICH E9 guideline a framework is introduced to help translating the trial objective into a precise definition of the treatment effect that is to be estimated. It aims to facilitate the dialogue between disciplines involved in clinical trial planning, conduct, analysis and interpretation, as well as between sponsor and regulator, regarding the treatment effects of interest that a clinical trial should address. The document aims at providing guidance in alignment of the choice of the estimand or estimands that reflect the primary trial objectives and which will form the basis to establish whether those objectives have been met (19).

Key findings in relation to outcome preferences detailed by regulators from the exploratory research completed to support this section of the toolkit are shown in Figure 1 below.

Figure 1. Exploratory research findings related to regulatory preferences for outcomes

Clinically and patient-relevant.			
EFFICACY Outcomes			SAFETY Outcomes
Clinical endpoints	Patient-reported outcomes	Surrogate outcomes	Safety
<ul style="list-style-type: none"> <li>• Trial endpoints</li> <li>• Detailed guidance in different disease areas.</li> </ul>	<ul style="list-style-type: none"> <li>• Accepted, but not usually primary endpoint</li> <li>• Disease-specific QoL instruments preferred (as more sensitive and may target factors relevant to a specific disease or patient)</li> <li>• Validated QoL instruments</li> <li>• Detailed guidance in different disease areas.</li> </ul>	<ul style="list-style-type: none"> <li>• Term 'surrogate' not generally used</li> <li>• All outcomes considered if they demonstrate a clinically relevant response.</li> <li>• Guidance on use of PFS in cancer.</li> </ul>	<ul style="list-style-type: none"> <li>• All safety outcomes/concerns</li> <li>• Includes any early or exploratory concerns</li> <li>• Established safety profile from one product in an indication may be utilised for other indications</li> <li>• Detailed guidance in different disease areas.</li> </ul>

### Potential implications for developers of COS

Regulatory outcome preferences are pre-specified in existing disease-specific guidance.

### Existing processes of selecting or specifying preferred outcomes

The outcomes and validated outcome measurement instruments that are preferred by regulators for a number of disease areas are outlined in the EMA's guidance in different disease areas. The guidance are harmonised across all European regulators and are regularly updated by the Committee for Medicinal Products for Human Use (CHMP). The CHMP also advises companies regarding new methods, including those related to outcomes such as validation of the use of a surrogate outcome through the EMA's Qualification of novel methodologies procedures (20). Regulators do not have a formal process for selecting and pre-specifying which outcomes are preferred for individual products, such as with a scope, as the criteria are pre-specified in the guidance.

## Acceptability of outcomes reported from RWE or big data

The use of outcomes reported from RWE has only been used in limited situations for the determination of efficacy to support marketing authorisation. Outcomes reported from RWE are more often used for pharmacovigilance purposes. No regulators had experience of the use of outcomes from big data to support marketing authorisation. There is currently no guidance from regulators regarding the use RWE or big data; however, a number of existing processes can be used to gain specific advice from regulators (formal scientific advice, EMA qualification of novel methodologies procedures, EMA Innovation taskforce). Some feedback from the exploratory research conducted to support this work related to RWE are summarised in Figure 2.

Figure 2. Quotes from the exploratory research on regulatory acceptability of outcomes from RWE or big data



## HTA agencies

### Background

[HTA is] 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 (24).

The HTA landscape for medicines in Europe is currently fragmented but a recent legislative proposal by the EC was adopted with the aim to establish a European system for HTA and harmonise HTA criteria in order to assess the added therapeutic value of medicines (21). Such a network with mandatory uptake of relative effectiveness assessments can have a major impact on transparency and policy in the future but will likely not be fully operational before 2024. At the moment there are at least 59 HTA agencies across European countries (22). Some have one national body where others have bodies that conduct assessments on a regional or hospital level. However, the focus on the patient is common theme among HTA agencies.

Broadly speaking, HTA agencies vary in their **role** with regard to:

- responsibility for regulatory and HTA assessment (some do both)
- the final decision for reimbursement or coverage (some provide a recommendation for the organisation that makes these decisions)
- involved in negotiating price (for some, this is done by the payer)
- the status of resulting decision following their assessment, some being statutory.

In addition, some countries do not use the term HTA but may have an organisation (s) that fulfil some or all of these functions.

### **Preferred outcomes**

Below were the findings regarding the outcomes preferred by HTA agencies examined through exploratory research. There were few differences between HTA agencies regarding outcome preferences, apart from the use of patient-reported QoL data. Acceptability of outcomes for all agencies is considered on a case-by-case basis and is often context specific.

Key findings in relation to outcome preferences detailed by HTA agencies from the exploratory research completed to support this section of the toolkit are shown in Figure 3.

Figure 3. Exploratory research findings related to HTA agency preferences for outcomes

Clinically and patient-relevant.			
EFFECTIVENESS Outcomes			SAFETY Outcomes
Clinical endpoints	Patient-reported outcomes	Surrogate outcomes	Safety
<ul style="list-style-type: none"> <li>• Longer-term final outcomes (i.e. overall survival)</li> <li>• Acceptability determined case-by-case.</li> </ul>	<ul style="list-style-type: none"> <li>• Most accept validated PROs</li> <li>• All accept and some require QoL</li> <li>• Some prefer disease-specific QoL instruments</li> <li>• Some prefer generic QoL instruments</li> <li>• Many determine acceptability of QoL instrument case-by-case (no stated preference)</li> <li>• Acceptability determined case-by-case.</li> </ul>	<ul style="list-style-type: none"> <li>• All agencies accept, if validated</li> <li>• Some are more open</li> <li>• Very few have specific guidance about how validation should be conducted.</li> <li>• Acceptability determined case-by-case.</li> </ul>	<ul style="list-style-type: none"> <li>• All require some safety</li> <li>• Range of requirements</li> <li>• No clear differences between agencies.</li> </ul>

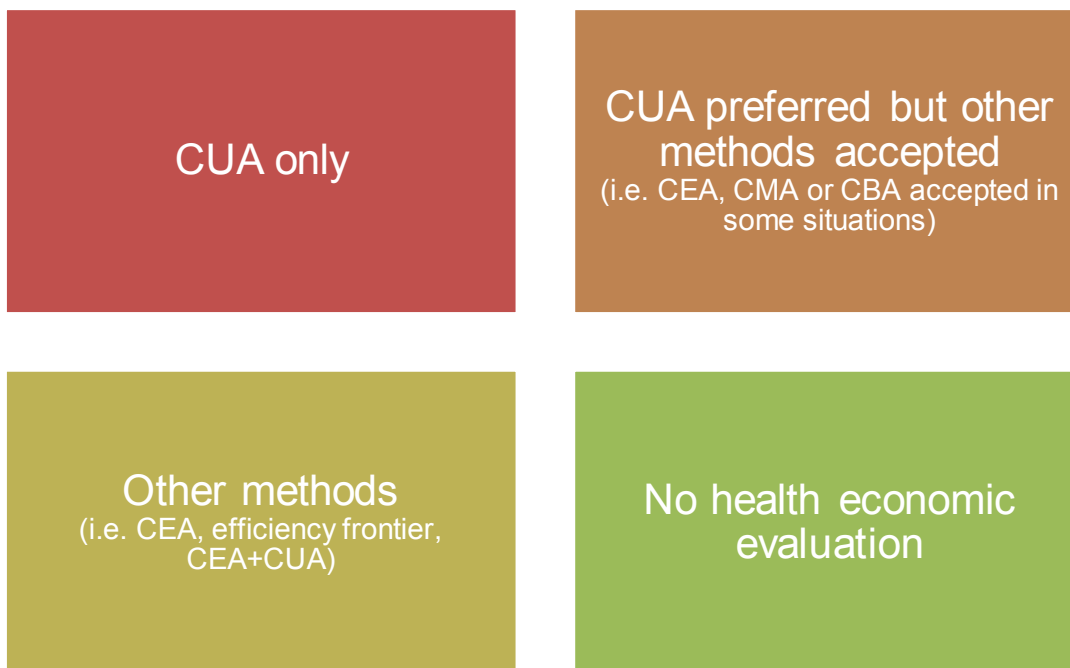
#### Potential implications for developers of COS

- As all HTA agencies require QoL to be reported, QoL should be included in COS.
- Longer-term or final outcomes are usually preferred by HTA agencies.
- PROs should be measured with validated instruments.
- Many outcome preferences are on a case-by-case basis.

## Methods

Most HTA agencies use some form of economic evaluation as part of their assessment to assess the value for money. Four main categories of HTA agencies emerged from the exploratory research, relating to methods for health economic evaluation (Figure 4). While many agencies had specific, stated preferences for certain methods, other methods were often accepted on a case-by-case basis.

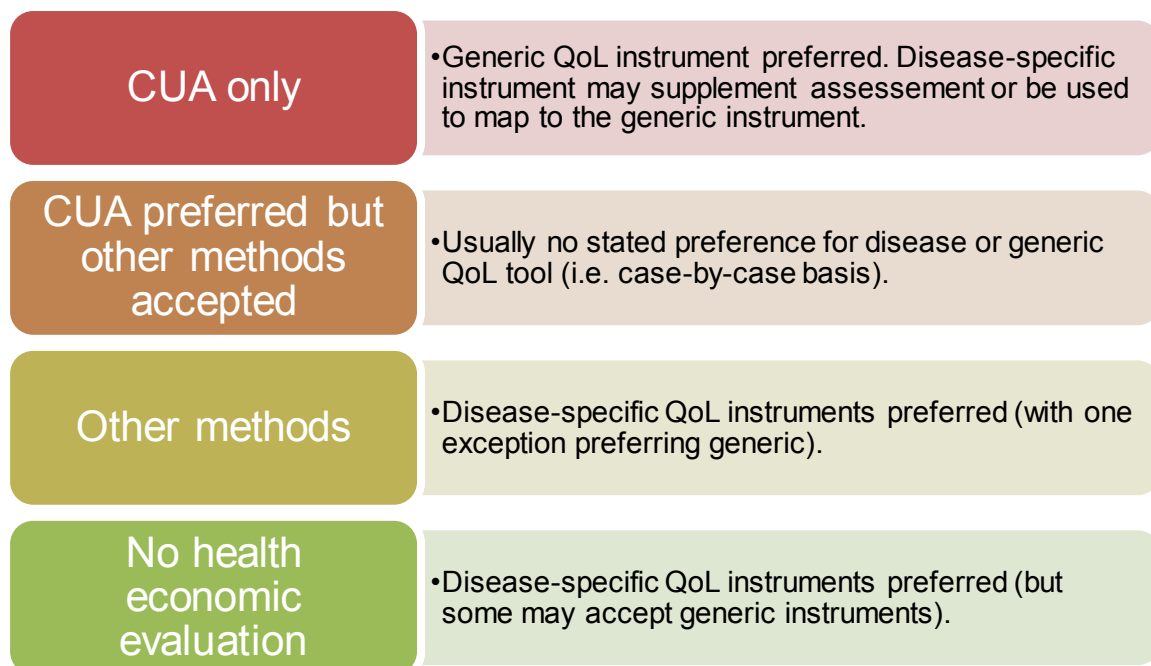
Figure 4. Four categories of HTA agencies from exploratory research



(Abbreviations: CBA – cost-benefit analysis; CEA – cost-effectiveness analysis; CMS – cost-minimisation analysis; CUA – cost-utility analysis. For a description of these methods see [Drummond 2005](#) or, for the efficiency frontier, see [IQWiG 2015 manual v4.2](#))

The work conducted showed some impact of the methods for economic evaluation on outcome preferences (see Figure 5).

Figure 5. Impact of economic evaluation methods on outcome preferences from exploratory research



**Potential implications for developers of COS**

Many methods preferences are on a case-by-case basis. However, differences from the exploratory work related to patient-reported QoL instruments indicate that including both a disease-specific and generic QoL instrument should be considered.

**Process of selecting or specifying preferred outcomes**

Only a small number of HTA agencies considered in the exploratory research select and then pre-specify which outcomes are preferred for individual products in some form of a scope.

For the identified agencies which select outcomes in a scope:

- the methods to select outcomes were usually case-by-case (including, for example, literature review, case law, internal meetings); most considered outcomes used in previous assessments in the same or a similar disease area
- none systematically considered existing COS
- only some involved public consultation
- only some actively involved patients or patient organisations (+ 1 included patient organisations in the public consultation on the whole scope).



For most HTA agencies that did not select outcomes themselves the outcomes are generally selected by the drug company. Some of these agencies will offer advice on outcomes prior to submission through informal processes but this is not routine practice.

Many agencies offer scientific advice for specific products (including with national regulators, with other HTA agencies or joint with the EMA), but the use of these processes is not routine.

There did not appear to be an impact of the process for selection of outcomes on outcome preferences.

### **Potential implications for developers of COS**

Publicly available scopes for products in the same or a similar disease area may be a useful source of information about an agency's outcome preferences.

### **Acceptability of outcomes reported from RWE or big data**

Some HTA agencies have had some experience with outcomes reported from RWE used to support estimates of a treatment's effect but this was only in a limited number of cases. No agencies had experience with outcomes reported from big data used to support estimates of a treatment's effect.

Most agencies noted that they expected to see more outcomes reported from RWE in future submissions, however, there was limited guidance available. The only guidance on the use of RWE was a technical support document that provided recommendations about the analysis and presentation of RWE was the Technical Support Document by the NICE Decision Support Unit (Faria 2015). This document summarises commonly available methods to analyse data from non-randomised studies to control for biases and proposes recommendations about improving the quality and transparency of assessments.

## ***Payers***

### **Background**

In addition to paying for healthcare, payers usually have a broader role in balancing the needs across the healthcare system or in their respective jurisdiction.

The diversity in payers across Europe is even greater than for HTA agencies. Payers may be also national, regional, or hospital-specific. Payers may have differing roles and responsibilities reflecting the differing healthcare system structure or respective processes for reimbursement.

### **Preferred outcomes**

Whether or not a payer has specific preferences for outcomes is likely to depend on their level of involvement in assessing the available evidence. The level of

involvement of payers in conducting HTA varies from some conducting the HTA themselves to others implementing decisions that HTA agencies make.

The exploratory research found that those who rely on an HTA agency to make the decision are likely to rely on HTA agencies to select and define outcomes. Those that conduct HTA are likely to consider longer term outcomes similar to HTA agencies, such as morbidity, overall survival, life-years gained and adverse events.

### **Acceptability of outcomes reported from RWE or big data**

Many payers appreciate that it is necessary for outcomes to be reported from non-randomised or RWE in some situations to support regulatory and HTA decisions where outcomes reported from RCTs are not available, such as for diseases with very small populations. However, a number of payers are concerned about RWE being used more widely and that they may replace RCTs which are necessary to provide unbiased estimates of effect.

### **Incorporating payer perspectives when developing COS**

As payers may be led by outcome preferences of the relevant HTA agency within a given jurisdiction or their preferences may be similar to HTA agencies (for those that conduct HTA), it may be more useful to engage with the relevant HTA agencies when developing COS.

### ***Patients***

This section gives an overview of factors influencing patients' and the public's decisions to share their data.

### **Factors influencing patients' and the public's decisions to share their data**

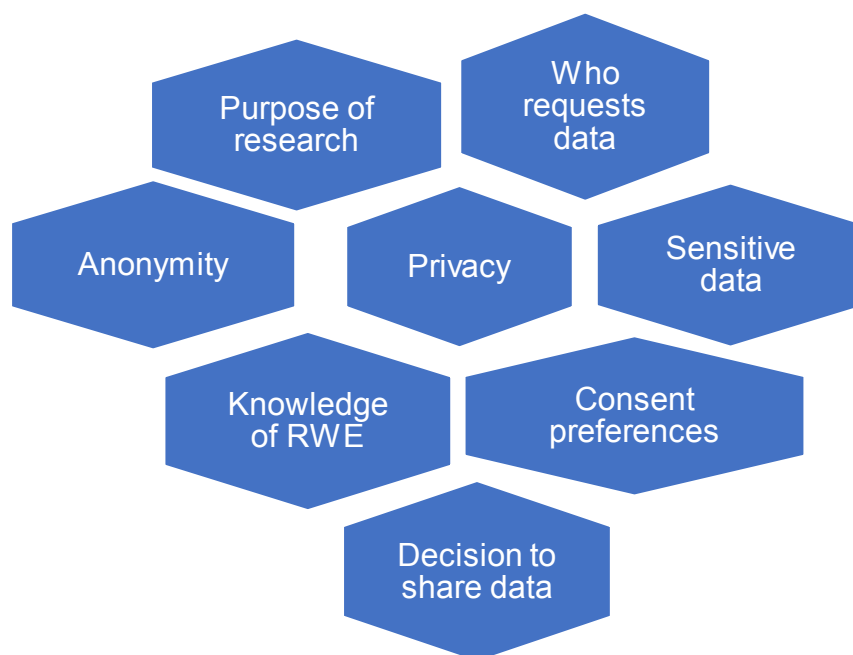
The use of RWE in health research is largely dependent upon patients consenting to share their EHR as well as insurance claims data, product and disease registries and health monitoring devices. The motivators and barriers for patients and the public in sharing their data may not influence the development of a COS directly but may need to be considered if developing a COS for prospective RWD collection where consent is required or if re-consent is required to utilise existing RWD for new research.

Figure 6 outlines some important factors influencing patients' decisions to share their data which may influence their willingness to share their data whereas Table 2 below highlights issues identified as important by patients and the public in making decisions about data sharing<sup>1</sup>.

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<sup>1</sup> This has been informed by a literature review undertaken by DO→IT task 2.2.5 (see Appendix E for more details).

Figure 6. Factors influencing patients' willingness for data sharing



In regards to the purpose of the research, epidemiological studies, studies to develop new treatments and broadly those that would benefit public health, were viewed in a positive light. Patients and the public generally felt more positive about sharing data for these purposes and felt less positive about sharing their data for profit orientated research. Requests to share data from certain stakeholders such as General Practitioners, the National Health Service (in a UK study) and patient advocacy groups encouraged data sharing while requests from pharmaceutical companies, insurance companies and distributed data networks did not. The studies reviewed found that patients and the public preferred to share their data if it were anonymous, particularly regarding sensitive data however many did not clearly understand the anonymization process or risks to identification which could persist even when data are anonymised. Feelings were mixed regarding the secondary use of de-identified data with some thinking this is acceptable and others thinking it was a breach of trust if consent was not regained. In regards to privacy, most of those in the studies reviewed thought a breach of privacy was highly unlikely but particularly serious. There was some confusion regarding risks to privacy whereby data sharing was considered risky but EHR more generally were not. In some studies reviewed, members of the public were anxious about how sensitively data on stigmatised would be handled. However in another study which compared the data sharing preferences of those with and without stigmatised illnesses, there were no differences between the groups. In many of the studies reviewed, participants had a poor understanding of what RWE was, however those with a better understanding of RWE were more inclined to be open to sharing their data. This suggests that improving awareness and understanding of RWE may be useful to encourage patients and the public to trust data sharing initiatives. Regarding consent, using opt-out and opt-out within a certain time frame as a proxy for consent was considered problematic. Some considered broad opt-in preferable to being contacted multiple times for re-consent while others thought this was necessary to ensure people can control what their data is used for.

Table 2. Overview of motivating and discouraging factors for data sharing

<b>Purpose of the research</b>	
✓ Causes of disease	✗ For profit
✓ Development of treatments	
✓ Benefit to public health	
<b>Who requests the data</b>	
✓ General Practitioners	✗ Pharmaceutical companies
✓ National health service	✗ Insurance companies
✓ Patient advocacy groups	✗ Distributed data networks
<b>Anonymity</b>	
✓ Happier to share more broadly if data are anonymised	✗ Unaware of anonymization processes
✓ Happier to share more sensitive information if anonymised	✗ Unaware of risks to identification when data are anonymised
✓ Some support secondary use of de-identified data	✗ Some opposed to secondary use of de-identified data
<b>Privacy concerns</b>	
✓ Security breaches considered unlikely	✗ Consequences of security breaches considered very serious
✓ Risks not considered as serious when sharing EHR to deliver care	✗ Unaware of data security practices
	✗ Large scale sharing considered more risky
<b>Sensitive data</b>	
✓ Some happy to share data even if illness stigmatised	✗ Some concerned about certain health conditions
	✗ Socio-economic data viewed as more sensitive in some cases
<b>Understanding of RWE</b>	
✓ Increased awareness associated with greater acceptance of data sharing	✗ Most had poor awareness of RWE
<b>Consent preferences</b>	
✓ Variation depending on whether data are identifiable	✗ Opt-out as a proxy for consent considered problematic
	✗ Mixed views on broad opt-in

Note: ticks (✓) indicate factors which influence data sharing while crosses (✗) indicate factors which influence reluctance to share data.

## References

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