Methods to assess and improve the uptake of core outcome sets

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

Karen Lindsey Hughes

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Abstract

Author: Karen Lindsey Hughes
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Introduction and aims
Core outcomes sets (COS) are agreed, standardised sets of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific area of health or health care. COS have the potential to reduce research waste by improving the selection and reporting of outcomes in randomised controlled trials (RCTs), but this reduction in waste will only be realised if researchers choosing outcomes for RCTs include COS in their studies. The continuous development of COS, without uptake, could itself result in research waste. This thesis examined the extent to which COS are used across different areas of health, also investigating the methods used to assess uptake, and explored barriers and facilitators to the implementation of COS to inform the development of interventions to improve uptake.

Methods
A systematic review to identify studies that had evaluated the uptake of a COS was undertaken. An assessment of citation analysis as an approach to assess COS uptake was carried out. A review of National Institute for Health Research Health Technology Assessment (NIHR HTA) RCT funding applications was undertaken, followed by a survey of chief investigators (CIs), to investigate the impact of a funder's recommendation to use COS. Qualitative interviews with CIs of NIHR HTA-funded RCTs explored the barriers and facilitators to COS uptake.

Results
The systematic review identified 26 studies that had assessed uptake of 17/337 (5%) COS. Uptake rates varied across health areas with 0% RCTs (gout) and 82% RCTs (rheumatoid arthritis) having measured the full COS. Variation was also found in the uptake of individual COS outcomes.
The assessment of citation analysis to evaluate COS uptake found that RCTs measuring the COS made up a small proportion of the citations received by COS reports. Not all RCTs citing a COS report measured all of the recommended outcomes. Some RCTs cited the COS reports for other design issues that had been addressed.
Ninety-five RCT funding applications submitted to the NIHR HTA for 2012-2015 were examined and nine applicants (10%) stated in their application that they had searched the Core Outcome Measures for Effectiveness Trials (COMET) Initiative database for a COS as recommended by the funder. In a follow up survey, a further eight applicants (8%) stated that they had searched the database. An additional 19 applicants (20%) searched for a COS using another source, e.g. a literature search.
Thirteen interviews were conducted with CIs of NIHR HTA-funded RCTs. Barriers and facilitators to COS uptake were identified relating to the behaviour of CIs, such as their awareness of COS, the characteristics of COS, such as patient burden, and the opportunities provided by organisations in the wider health research system, such as funders.

Conclusions
Few studies have assessed the uptake of COS and further studies are needed across more areas of health. Funders of RCTs can have an impact on the uptake of COS but more steps can be taken to increase this impact. The barriers and facilitators to COS uptake can be addressed by behaviour change interventions, the COS development process and the wider research system.

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Abbreviations

BCW	Behaviour Change Wheel
CI	Chief Investigator
COM-B	Capability, Opportunity, Motivation-Behaviour
COMET	Core Outcomes Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcome Set(s)
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
CROWN	Core Outcomes in Women's Health
DFG	Deutsche Forschungsgemeinschaft
EMA	European Medicines Agency
EBM	Evidence Based Medicine
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
EViR	Ensuring Value in Research
FDA	Food and Drug Administration
HOME	Harmonising Outcome Measures for Eczema
HRB	Health Research Board
HTA	Health Technology Assessment
KCE	Belgian Health Care Knowledge Centre
ICTMC	International Clinical Trials Methodology Conference
ILAR	International League of Associations for Rheumatology
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
OMERACT	Outcome Measures in Rheumatology
PCORI	Patient-Centered Outcomes Research Institute
PedIMMPACT	Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
PICO	Population/Intervention/Comparator/Outcome
RCT	Randomised controlled trial
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Randomised controlled trials

Randomised controlled trials (RCTs) are health research studies that provide valuable evidence as to the safety and effectiveness of health care interventions (1). Under the RCT design, participants are randomly allocated to a group that will receive either the intervention under investigation or a comparator/no intervention. This randomisation of participants is a key feature of the RCT design as it ensures that any participant characteristics that may have an effect on the assessment of the intervention, such as age or clinical history, will be balanced across the groups and any differences reported between the groups can be attributed to the intervention (2).

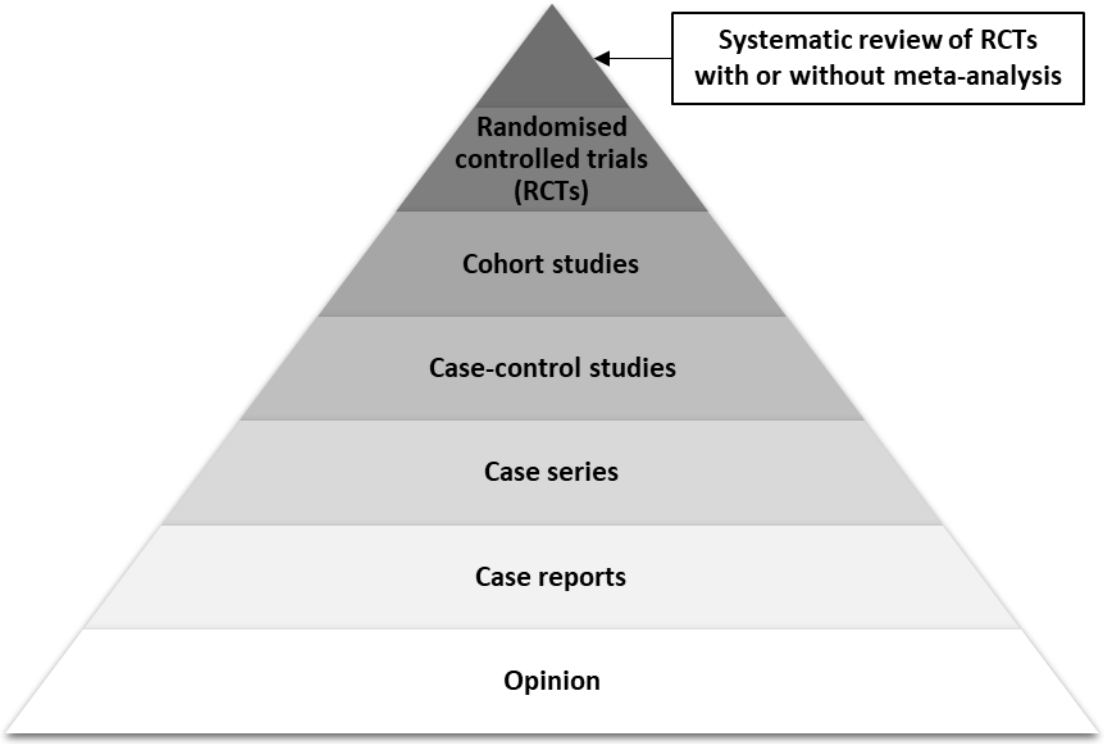
In designing RCTs, researchers often draw on the PICO framework which was developed to support the structuring and focus of clinical questions (3). In RCTs the study population (P) is allocated to receive the intervention (I) being investigated or the standard comparator (C) or no intervention. The effect of the intervention can then be assessed by measuring differences in patient outcomes (O) between the groups (Figure 1).

Figure 1: The PICO framework

Because of the strength of the evidence that RCTs are able to generate by reducing bias through randomisation, they play a key role in Evidence Based Medicine (EBM). EBM aims to support those making decisions about health care to ensure that patients receive the best possible clinical care. This is done by combining individual clinical expertise with the best available evidence from health research (4). To assist health care professionals, patients and others making decisions about health care to access the best research evidence to inform

their decisions, hierarchies have been suggested that rank research designs depending on their risk of bias. The hierarchies are typically presented in a pyramid to demonstrate the risk of bias reducing from the bottom to the top. Such a hierarchy was suggested by Akobeng (1) as presented in Figure 2. In this hierarchy Akobeng suggests that the strongest evidence comes from RCTs or systematic reviews that bring together the results of all relevant RCTs.

Figure 2: Hierarchy of research evidence to evaluate health care interventions. Adapted from Akobeng (1).



1.2 The importance of outcomes in RCTs

An outcome in an RCT is a measurement or event that may be affected by the intervention being studied (5). For example, in an RCT evaluating an intervention for low back pain the investigators may choose the level of pain that participants experience as an outcome to assess of the effectiveness of the intervention. Alongside outcomes that demonstrate effectiveness, investigators should also measure outcomes that reveal any adverse events related to the intervention. As demonstrated by the PICO framework, the effect that an intervention has on outcomes will be used to determine whether it is safe and effective. Given that the results produced by RCTs based on an assessment of outcomes can inform

health care practice and policies as part of evidence based medicine, it is crucial that careful attention is paid to the selection of outcomes for an RCT. Inadequate consideration of the selection and reporting of appropriate outcomes in RCTs can lead to significant problems.

1.3 The problem with outcomes in RCTs

1.3.1 Inconsistency

As shown in Figure 2, systematic reviews of RCTs are ranked as providing the highest level of evidence that can support decision making in health care. Although RCTs are often referred to as the 'gold standard' for assessing interventions, it is recognised that a single RCT is not likely to result in a change to practice (6). Therefore, systematic reviews are vital for bringing together all of the available evidence generated by RCTs. However, this process of pooling evidence is hindered if the RCTs have measured different outcomes in different ways. Inconsistency in outcome selection and measurement is not confined to a single area of health and there is evidence that this is a problem across a spectrum of clinical areas. For example, a systematic review of the primary outcomes used in RCTs for pre-term birth prevention found that the 103 RCTs identified between 1997 and 2011 reported 72 different primary outcomes (7). In a cohort of 8,942 oncology RCTs identified between October 2007 and September 2010, researchers discovered over 25,000 outcomes that occurred only once or twice (8). Furthermore, a systematic review investigating outcomes used to assess cosmesis following breast reconstruction surgery identified inconsistencies in the methods used to assess cosmesis and the decision as to who should make the assessment (9). Such inconsistencies hamper the efforts of systematic reviewers who strive to synthesise results from RCTs to strengthen the evidence available for making decisions about health care interventions.

1.3.2 Outcome reporting bias

Outcome reporting bias occurs when a subset of the outcomes that were measured in an RCT are selected to be reported based on their results (10). Research has shown that statistically significant results are more likely to be reported than non-significant results which could lead to the effects of interventions being overestimated (11). A review carried out in 2008 examined studies that had assessed outcome reporting bias in RCTs. When looking for discrepancies between the outcomes that had been prespecified in RCT study protocols and the outcomes reported in the RCT publications it was found that 40-62% of

RCTs had changed, introduced, or omitted a primary outcome (12). Another study investigated the impact of outcome reporting bias in RCTs on systematic reviews. The authors found that after adjusting for outcome reporting bias 19% of the reviews with a statistically significant result would have become non-significant and a further 26% had overestimated the treatment effect by at least 20% (13). Without the full reporting of outcome data from RCTs, the users of RCT reports and systematic reviews will not have the necessary evidence to reach a fully informed decision about health care interventions.

1.3.3 Relevance to patients

In order to effectively evaluate a health care intervention, it is necessary to include outcomes that are meaningful to patients in the assessment (14). However, studies have shown that outcomes that are important to patients are often overlooked. For example, a systematic review of patient-important outcomes, defined as outcomes that patients value, in endocrine-related illnesses found that only 30% of RCTs assessed had included such outcomes (15). Furthermore, a study that extracted details of patient reported outcomes from RCTs for cardiovascular disease found that 70% of the RCTs did not report patient reported outcomes that would have given an insight into the patients' perspective of the intervention (16).

1.4 How COS address the problems with outcomes in RCTs

COS have been defined as agreed, standardised sets of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific area of health or health care (17). COS address the problems relating to the selection and reporting of outcomes in RCTs. For example, if all RCTs for the same health condition select the same core set of outcomes, the consistency of outcomes measured across RCTs will improve. As well as recommending 'what' outcomes to measure, some COS also recommend 'how' to measure them. This standardisation of outcomes will in turn assist with the pooling of results from different RCTs. It is important to note that the outcomes recommended by a COS are the minimum that should be implemented and using a COS does not prevent the inclusion of additional outcomes that may be relevant to a particular RCT (18). It should also be noted that there may be cases where it is reasonable not to use a COS, for example where the scope of the COS does not match with the scope of the RCT in terms of the intervention or population for which the COS was developed.

In addition to improvements in consistency, the use of COS can also address outcome reporting bias. All of the outcomes recommended by a COS should be reported by RCTs and so the selective reporting of outcomes should be reduced. Furthermore, it is recommended that patients, their carers and members of the public are included as stakeholders in the development of COS (19). This ensures that the outcomes measured in an RCT will include those that are important to people who have direct experience of the health condition (20).

While COS have been developed for a variety of settings outside of RCTs, for example, routine clinical practice and research registries, the focus of this thesis is on those COS that have been developed for effectiveness RCTs. Unlike efficacy, or explanatory, RCTs that aim to determine the effects of an intervention under ideal conditions, effectiveness, or pragmatic, RCTs aim to determine the effects of an intervention in routine clinical practice (21). Effectiveness RCTs use outcomes that are often used in routine practice as opposed to the laboratory-based outcomes used in efficacy RCTs (22).

In recent years the number of COS has grown significantly (23-29) and if implemented, COS can help to reduce waste in research that would result from the poor selection and reporting of outcomes in RCTs.

1.5 Waste in research

Research waste is produced through the poor design, conduct and reporting of health research studies (30) and it has been suggested that 85% of global health research funding is wasted (31). In 1994 Altman drew attention to the "scandal" of research waste and called for action that would lead to "less research, better research, and research done for the right reasons" (32).

Recommendations for reducing research waste were made in a 2014 Lancet Series. These included more attention being paid to setting priorities for research (33) and improvements to research design, conduct, and analysis (34), the regulation, governance and management of research (35) and the accessibility and reporting of research (36, 37).

Several initiatives have been launched in a bid to reduce waste in health research. The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network is an

initiative that has developed a range of reporting guidelines for health research studies including the Consolidated Standards of Reporting Trials (CONSORT) Statement for reporting RCTs (38). In 2013 the AllTrials initiative (https://www.alltrials.net/) was formed to campaign for the registration of all past and present RCTs on a global scale, including the reporting of their methods and results, and more recently the Ensuring Value in Research (EViR) Funders' Forum was launched to bring together funders to develop methods to reduce research waste (39).

COS can contribute to the efforts to reduce waste in research by addressing the problems with outcomes in RCTs that may lead to waste, i.e. results being excluded from evidence synthesis due to inconsistencies in outcomes, the selective reporting of outcomes and patient-important outcomes being overlooked. However, this will only be achieved through the uptake of COS by clinical trialists. Moreover, if COS continue to be developed without subsequent uptake, this will itself lead to research waste as a result of funding and time being invested in an initiative that is not then implemented. It is therefore necessary to take steps to assess and maximise the uptake of COS in RCTs.

1.6 The need for research into methods to assess and improve the uptake of COS

As described in the preceding sections of this chapter, COS have the potential to reduce waste in research by addressing problems with outcome selection and reporting in RCTs. However, this potential will only be realised through the uptake of COS by clinical trialists.

1.6.1 Uptake of initiatives in health research

It has been documented that uptake of initiatives in health research is often insufficient. For example, despite the quality of evidence produced by systematic reviews (Figure 2), it has been found that their application to inform clinical guidelines and routine practice is limited (40). A study published in 2015 examined whether relevant systematic reviews that had included IPD meta-analysis, which uses original research data rather than summary findings from study reports, had been used to inform a sample of 177 clinical guidelines. The findings revealed that only 37% of the guidelines had cited a relevant IPD meta-analysis and 27% had based their recommendations on the IPD meta-analysis (40). Investigation into the barriers that impede uptake of evidence from systematic reviews by end users, including health care

professionals and policy makers, suggested that lack of awareness, access, familiarity, perceived usefulness and motivation all play a part (41).

Alongside the limited use of systematic reviews to inform clinical guidelines, the guidelines themselves suffer from a lack of uptake in practice across different clinical areas. During an audit of 66 adult intensive care units it was determined that only 24% of patients received care that was fully compliant with the relevant clinical guideline (42). In a survey completed by hospitals and obstetricians, the majority of responders (87-94%) indicated that they were aware of guidelines recommending a reduction in the use of caesarean sections and most (82.5-85%) agreed with the guidelines. Furthermore, one third of hospitals and obstetricians reported a decline in caesarean section rates. However, in practice data revealed that after the publication of the guidelines caesarean section rates were 15-49% higher than had been reported (43). A study that examined the uptake of National Institute for Clinical Excellence (NICE) guidelines through surveys, interviews and a review of case notes found variation in uptake. Whilst some practices were consistent with NICE recommendations, others were not, and in some cases the guidelines did not show any effect on practice (44).

Given that clinical guidelines support the translation of research evidence into clinical practice (45), poor uptake results in a gap between what is being suggested by the current best available evidence and what is happening clinical practice. To address the lack of uptake, studies have been carried out to investigate potential barriers. One such systematic review identified barriers to uptake of guidelines by nurses. These related to what were categorised as ‘internal’ factors, such as nurses’ attitudes, perceptions and knowledge, and ‘external’ factors, such as the usability of the guidelines, resources and leadership (46). Research into the uptake of stroke clinical guidelines reported similar barriers, i.e. inadequate resources, poor guideline characteristics and inadequate training and education (47). Another systematic review that brought together studies that had considered the barriers to uptake of guidelines across different clinical areas, found three levels across which barriers could be defined (48). These were ‘personal’ factors, such as physicians’ knowledge and attitudes, ‘guideline-related’ factors, such as plausibility of recommendations, access to guidelines and poor layout, and ‘external’ factors such as lack of resources and organisational constraints.

1.6.2 Initiatives to improve uptake of COS

As with systematic reviews and clinical guidelines, it is important to assess the uptake of COS across different areas of health and identify barriers and facilitators to inform strategies to improve uptake. Various disease specific initiatives have been formed to promote the development and uptake of COS in a particular clinical area. The Outcome Measures in Rheumatology (OMERACT) Initiative was launched in 1992 and aims to improve the measurement of outcomes in rheumatology (49). Since its launch, OMERACT has published a handbook and guidance documents to assist COS developers in choosing what outcomes to measure and how to measure them. OMERACT supports the involvement of patients in COS development (50) and has investigated methods to improve the uptake of OMERACT COS (51). Likewise, the Harmonising Outcome Measures for Eczema (HOME) Initiative brought together patients, health care professionals, journal editors, regulatory authorities and the pharmaceutical industry on a global scale in the development of a COS for eczema (52). HOME has developed a methodological framework to assist COS developers in the development and implementation of COS (53). Following recognition of the inconsistency that exists in outcomes across RCTs in women's health, the Core Outcomes in Women's Health (CROWN) Initiative was formed. CROWN is a consortium of gynaecology-obstetrics and related journals that have come together to promote the development, uptake and reporting of COS in women's health (54).

In 2010 the Core Outcomes Measures in Effectiveness Trials (COMET) Initiative was launched to promote the development and uptake of COS across all clinical areas (55). To facilitate this, COMET hosts a searchable database (https://www.comet-initiative.org/Studies) that brings together all published and ongoing COS studies, identified by a systematic review with annual updates (23-29), in a central location. This reduces the duplication of COS development in areas where they already exist and assists clinical trialists in their search for a relevant COS. COMET has published a handbook that offers recommendations for the COS development process (17) and has supported the production of a set of minimum standards for COS development (19). COMET has also built links with a range of organisations, including funders of RCTs, journal editors, and trial registries who now endorse COS (https://www.comet-initiative.org/COSEndorsement).

1.6.3 Rationale for the thesis

There are currently 370 published COS studies (29) and 341 ongoing COS studies registered with the COMET Initiative database as of February 2021. Due to the growing number of COS, it is important to ensure their uptake so they contribute to reducing research waste and to prevent further waste through lack of implementation.

The use of COS is not routinely required to be reported in a registry or RCT report. In order to encourage the assessment of COS uptake in RCTs, it is necessary to provide an efficient method to do so that is not resource-intensive and is based on up to date information. The methods that have previously been used to assess COS uptake have been unable to satisfy these requirements and further work is needed to develop a suitable method to assess uptake of COS in RCTs.

Research into other initiatives in health research has shown that uptake is often lacking, and while various strategies to encourage the uptake of COS have been put in place, it is necessary to assess the impact of the current strategies. Furthermore, in order to suggest the most appropriate interventions to improve COS uptake, an exploration of the barriers and facilitators to uptake from the perspectives of the clinical trialists who will use them is needed.

This thesis presents an investigation of methods to assess and improve the uptake of COS in RCTs. The specific research questions addressed are:

- To what extent are COS used in RCTs across different areas of health?
- Is citation analysis an efficient method to assess COS uptake in RCTs?
- Can a funder of RCTs have an impact on COS uptake?
- What are the barriers and facilitators to COS uptake by clinical trialists?

1.7 Thesis structure

Chapter 2 presents a systematic review that brought together studies that had assessed uptake of a COS within RCTs or systematic reviews. The review involved the exploration of the level of uptake across different COS, and different areas of health, alongside the identification of methods that had been used to assess the uptake of COS, and the perceived barriers to uptake.

Chapter 3 reports an investigation of citation analysis as an approach to assess the uptake of COS. Previous methods for assessing uptake have proven to be resource-intensive. We evaluated whether the number of citations received by a COS report could be reasonably taken as a surrogate measure of its uptake in RCTs.

Chapter 4 presents an assessment of the impact that a funder of RCTs can have on uptake of COS by recommending to their applicants that they be considered for inclusion. An examination of National Institute for Health Research Health Technology Assessment (NIHR HTA) funding applications was carried out to identify whether or not applicants had considered a COS. This was followed by a survey of NIHR HTA chief investigators (CIs) to further explore their consideration and use of COS.

Chapter 5 presents a qualitative interview study carried out with CIs of NIHR HTA-funded RCTs. The study drew on implementation science and explored the barriers and facilitators to COS uptake from the perspective of those with experience of choosing outcomes for RCTs.

Chapter 6 provides a summary of the findings from the previous chapters, the implications of those findings and suggestions for future work.

1.8 Terminology

For the purposes of this thesis, the following terminology relating to COS is used:
'Outcome' is used in relation to 'what' will be measured, for example, pain.
'Outcome measurement instrument' is used in relation to 'how' an outcome is measured, including any definitions and measurement tools such as a questionnaire or a machine.

Chapter 2: A systematic review of core outcome set uptake

Preface

Chapter 2 presents a systematic review that was carried out to explore the uptake of COS within RCTs and systematic reviews. The review has been published in the Journal of Clinical Epidemiology (56) (Appendix 1) and sections of this chapter have been taken directly from the published manuscript. Karen Hughes carried out the data collection and analysis and wrote the original draft of the manuscript, which was edited by senior authors and has been subject to peer review.

2.1 Background

As described in Chapter 1, COS have the potential to reduce waste in research by improving the consistency, relevance and reporting of outcomes measured in RCTs. However, patients, healthcare professionals and all other end users of RCT results will only benefit from COS if researchers choosing outcomes for RCTs include them in their studies. In addition, there is a danger that the continuous development of COS, without uptake, will itself result in research waste, contrary to the rationale for COS.

It is therefore important that COS developers consider what steps they can take to increase uptake of their COS and monitor its use to establish whether uptake is being achieved. Assessing the uptake of COS in RCTs, or systematic reviews of RCTs, offers COS developers the opportunity to revisit their strategies for promoting uptake where this is found to be low. An assessment of uptake can also allow developers to review the relevance of their COS. For example, if outcomes in the COS are not being used, or RCTs are consistently measuring an outcome that does not appear in the COS, an update may be suggested.

2.2 Aims

As the number of COS continues to grow, the aim of this review was to identify studies that have evaluated the uptake of a COS, explore the level of uptake across different areas of health, and review the methods used to assess uptake.

2.3 Methods

2.3.1 Identification of relevant studies

Citation analysis

Studies were identified by reviewing the citations received by articles reporting a COS published between 1981 and July 2016. The rationale for this method was that a study assessing uptake of a COS should cite the publication reporting that COS. We set this timeframe because the first COS article that we are aware of was published in 1981 and we started accessing citation reports in July 2018. A cut-off date of July 2016 for the publication of the COS was likely to allow sufficient time for the COS to be cited in an uptake study. We included 337 COS publications (Appendix 2) identified from the COMET Initiative's systematic reviews that had been published at the time of data collection (23-28). We accessed the citation reports for each COS publication using Scopus, which has been found to include more articles for citation analysis than Web of Science and is more up to date than Google Scholar (57).

Scopus alerts

To ensure that this review remained current, an alert was set in Scopus to capture studies of COS uptake published after July 2018 that would not appear in the citation search.

2.3.2 Inclusion and exclusion criteria

Studies were included if they had assessed the uptake of the outcomes recommended by the COS, either individually or as a full set, by RCTs or systematic reviews. If studies had assessed uptake in additional types of study, e.g. observational studies, we only included data for the RCTs and systematic reviews in the results. We included studies that had reported data that allowed the COS uptake rate to be calculated, even if COS uptake was not the main purpose of the study. Studies were ineligible if they had assessed uptake of outcome measurement instruments without an assessment of the recommended outcomes. Studies were excluded if they had not assessed uptake of all of the outcomes in the COS, e.g. if they had only assessed uptake of the patient reported outcomes recommended by the COS, in order to ascertain the level of compliance with the full recommendations of the COS and make comparisons across health areas.

2.3.3 Selecting studies for inclusion

The references and abstracts of all publications that had cited the 337 COS articles were identified using Scopus and exported into Microsoft Excel. If a reference appeared more than once in the Excel file, because the publication had cited more than one COS article and therefore appeared in more than one COS article's citation report, we removed the duplicate references. We searched the titles of each citing publication using keywords (Appendix 3) relating to COS and uptake to identify possible studies of COS uptake. The resulting titles were assessed, followed by a review of the abstract for those judged to be possible studies of COS uptake. Full texts were examined for those where it was judged from the abstract that the publication may be reporting an assessment of the uptake of a COS or where an abstract was not available. The references in each of the eligible studies were checked for further studies of COS uptake.

2.3.4 Checking for correct exclusion

To confirm the assessment of titles by the first reviewer (Karen Hughes: KH), a second reviewer (Paula Williamson: PW) independently assessed 50 titles. As complete agreement was reached on inclusion and exclusion of articles at this stage, KH completed the rest of the title assessments. PW reviewed 20 abstracts and agreed with KH's assessment, who then completed this stage. The full texts of 10 articles excluded at title stage and 20 articles excluded at abstract stage were checked by KH for correct exclusion.

2.3.5 Data extraction

For each eligible study, the following data were extracted and recorded in a data collection form: disease category, disease name, scope of the uptake study, period covered by the assessment, number of RCTs/systematic reviews assessed, % RCTs/systematic reviews that measured the full COS and/or % RCTs/systematic reviews that measured each individual outcome in the COS, the method used to assess uptake and suggested barriers and facilitators for uptake. The scope was defined in terms of the population with the health condition and/or intervention type for which RCTs/systematic reviews were identified and assessed for COS uptake.

2.3.6 Data analysis

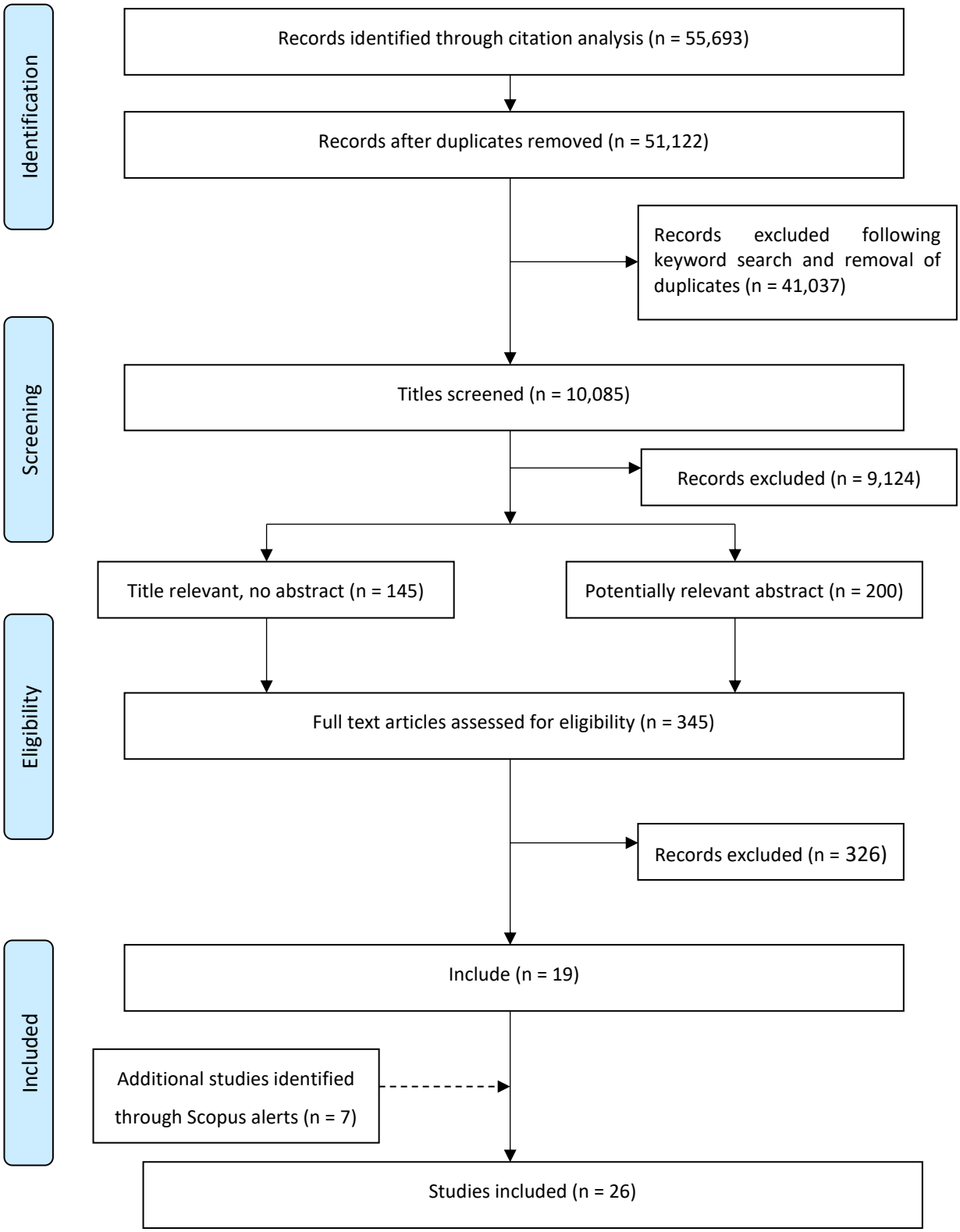
The results of the review are presented descriptively. We did not carry out any statistical analyses to synthesize the data.

2.4 Results

2.4.1 Studies identified

The 337 COS publications received a combined total of 55,693 citations with 51,122 remaining once duplicates had been removed. The titles of 10,085 of the citing articles contained at least one of the keywords. Following the screening of titles and abstracts, 345 full texts were examined, including articles that had no abstract, leading to the identification of 19 studies of COS uptake (Figure 3). A further seven studies were identified via Scopus alerts. We did not identify any additional studies after checking the references of the included studies. Four studies were excluded because they did not assess uptake of all outcomes that were recommended by the COS. One of these studies assessed uptake of a resource use outcome only, while another assessed only uptake of the patient reported outcomes recommended by the COS. A third study focused on measurement instruments and included an assessment of uptake of some, but not all, COS outcomes and the final study assessed uptake of a selection of outcomes from a COS that is made up of 48 recommendations. Appendix 4 shows the references of all included studies and the COS they assessed. The 26 studies assessed uptake for a total of 17 COS, with five COS being assessed by more than one study. Thus, we found that 17/337 (5%) COS had been assessed for uptake.

Figure 3: Identification of studies



2.4.2 Description of studies

Twenty-four studies assessed uptake in RCTs and two studies assessed uptake in systematic reviews (Table 1). The COS assessed were published between 1982 and 2014 and recommended between one and 19 outcomes, with the majority (n = 12; 71%) comprising of seven outcomes or fewer. The studies assessed between eight and 382 RCTs and the two assessing systematic reviews included 48 and 90. The 26 studies covered five of 31 disease categories where COS have been developed (Figure 4). Just over half of the studies (n=14) assessed uptake of a rheumatology COS. The other studies assessed uptake of COS developed in the categories of anaesthesia and pain control (n=7), orthopaedics and trauma (n=3), neurology (n=1) and skin (n=1).

Table 1: Studies assessing uptake of COS in RCTs and systematic reviews

COS disease category	COS disease name	Year COS published	No. outcomes in COS	Scope of uptake study	Period assessed for uptake of COS	No. RCTs assessed	% RCTs measuring each COS outcome	% RCTs measuring full COS
Rheumatology	Psoriatic arthritis	2007	6	Psoriatic arthritis[A4]	2006 – 2010	17	77, 71, 59, 53, 47, 47	24
				Psoriatic arthritis[A13]	2010 - 2015	22	100, 95, 91, 86, 82, 77	59
	Knee, hip, and hand osteoarthritis	1997	5*[1]	Trapeziometacarpal osteoarthritis[A5]	- 2010	316*[2]	96, 94, 67, 59, 4	-
			3 + 1 (≥ 1 year)	Total knee anthroplasty[A16]	- 2014	30	93, 27, 10*[3]	7
				Hip or knee osteoarthritis[A23]	1997 - 2017	382	95, 86, 75, 48	45
				Osteoarthritis[A25]	2012 – 2017	334	97, 84, 17, 30	14
	Rheumatoid arthritis	1982*[4] 1989	10 7	DMARD therapy for rheumatoid arthritis[A1]	1986 – 1990	32	100, 91, 91, 91, 91, 73, 73, 64, 55, 55 100, 91, 91, 91, 73, 55, 27	-
		1994	7 + 1 (≥ 1 year)	Rheumatoid arthritis[A2]	2005 – 2007	50*[5]	-	82
				Rheumatoid arthritis[A6]	- 2009	350		60-70*[6]
				Rheumatoid arthritis[A17]	2002 – 2016	143	-	81
				Rheumatoid arthritis[A22]	2009 - 2019	197	-	Just over 80
	Ankylosing spondylitis	1997	6 (SMARD) 9 (DC-ART)	Ankylosing spondylitis/axial spondyloarthritis[A7]	- 2013	99	92, 84, 77, 51, 46, 44 97, 97, 92, 84, 82, 79, 68, 63, 16	20
	Acute and chronic gout	2009	5 (acute)	Acute gout[A8]	- 2011	77*[7]	99, 57, 51, 32, 5	-
		2005	5 (acute) 9 (chronic)	Acute and chronic gout[A11]	- 2013	38*[8] 30*[8]	87, 79, 71, 29, 8, 80, 73, 70, 10, 7, 3, 0, 0, 0	5 0

Anaesthesia & pain control	Chronic pain	2008	19	Cognitive and/or behavioural treatment[A3]	- 2010	60	94, 83, 12 outcomes >40, 5 outcomes 0	-
		2003	6	Acceptance and Commitment Therapy[A9]	1999 - 2014	10	90, 90, 80, 70, 10, 10	-
				Burning mouth syndrome[A21]	1994 – 2017	36	100, 97, 78, 33, 28, 22	11
		2003 2008 (update)	6 3	Opioids for chronic non-cancer pain[A10]	- 2012	156	99, 94, 76, 46, 43, 31, 28, 19, 7	-
	Pediatric acute and chronic pain	2008	6	Postoperative pain management[A18]	- 2017	337	93, 83, 21, 16, 15, 15	-
Orthopaedics & Trauma	Fall injury	2005	5	Fall prevention in older people[A14]	2005 – 2015	34	94, 47, 24, 24, 21	3
	Spinal cord injury	2007	1	Anticholinergic therapy for neurogenic bladder in SCI[A15]	1946 – 2015	14	3	3
	Hip fracture	2014	5	Hip fracture[A24]	1997 – 2018	311	47, 46, 41, 37, 29	12
Neurology	Peripheral neuropathy	2006	3	Multifocal motor neuropathy[A12]	1995 – 2014	8	100, 100, 13	13
Skin	Eczema	2011	4*[9]	Atopic eczema treatments[A26]	2005 – 2018	177	-	25%*[10] 33%*[11]
						No. SRs assessed	**% SRs measuring each COS outcome**	**% SRs measuring full COS**
Anaesthesia & pain control	Chronic pain	2003	6	Neuropathic pain conditions[A19]	- 2015	90	94, 84, 53, 50, 49, 29	10
	Pediatric acute and chronic pain	2008	6	Postoperative pain[A20]	- 2017	48	88, 75, 29, 21, 19, 15	-

*[1] assessed all 4 inner core outcomes plus 1 middle core outcome

*[2] includes RCTs and observational studies

*[3] Uptake of 1 outcome not reported individually but included in full uptake assessment

*[4] Study included 2 COS

*[5] Excluded trials from assessment if they did not report at least 1 patient reported outcome (PRO)

*[6] in 2009

*[7] Excluded trials from assessment if they did not report at least 1 core outcome

*[8] includes quasi-RCTs (3 acute, 2 chronic)

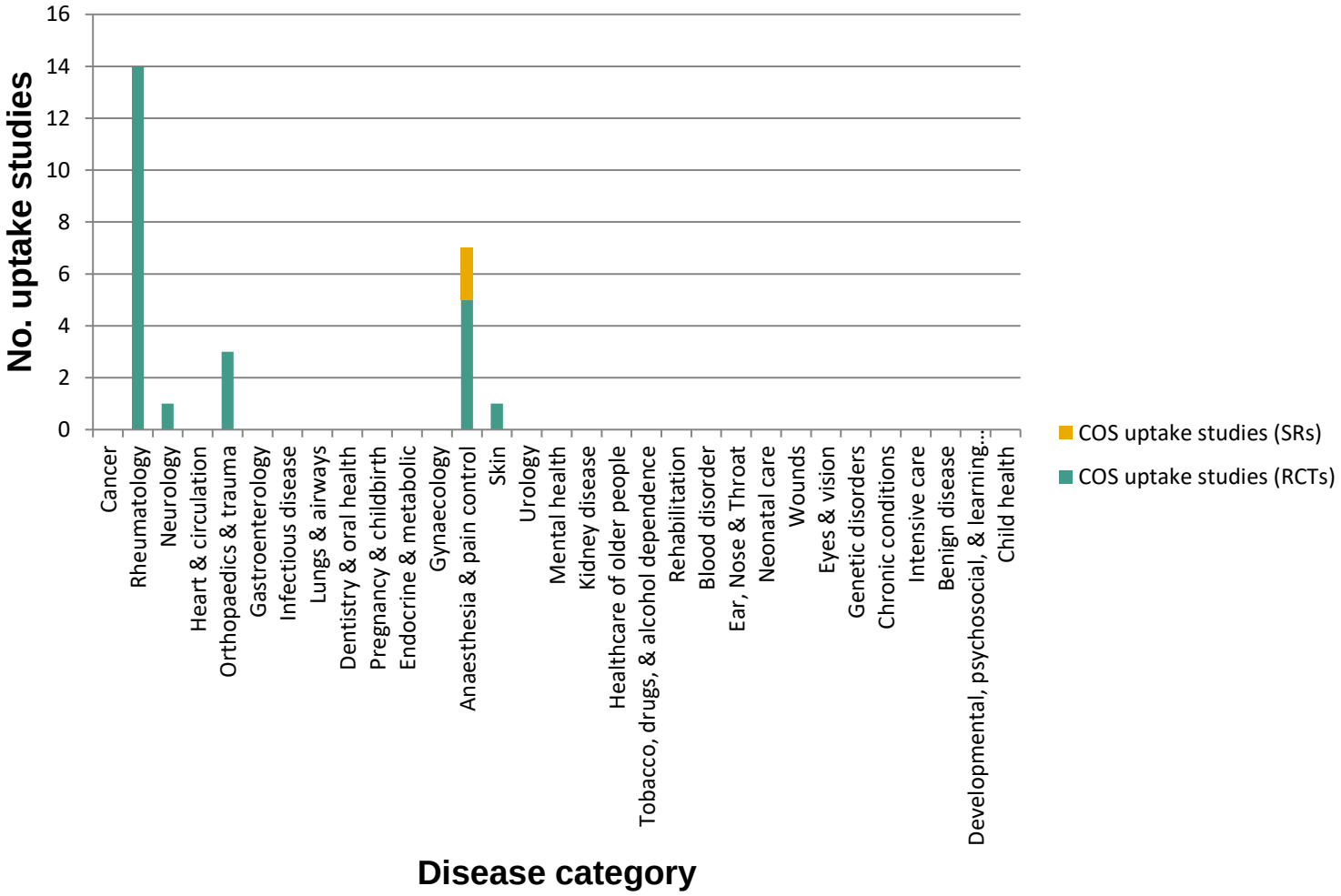
*[9] 3 outcomes assessed as 1 outcome not defined at time of review

*[10] Average from 2005 – 2018

*[11] in 2018

[A1-A26] corresponds to uptake study listed in Appendix 4

Figure 4: Number of COS uptake studies by disease category



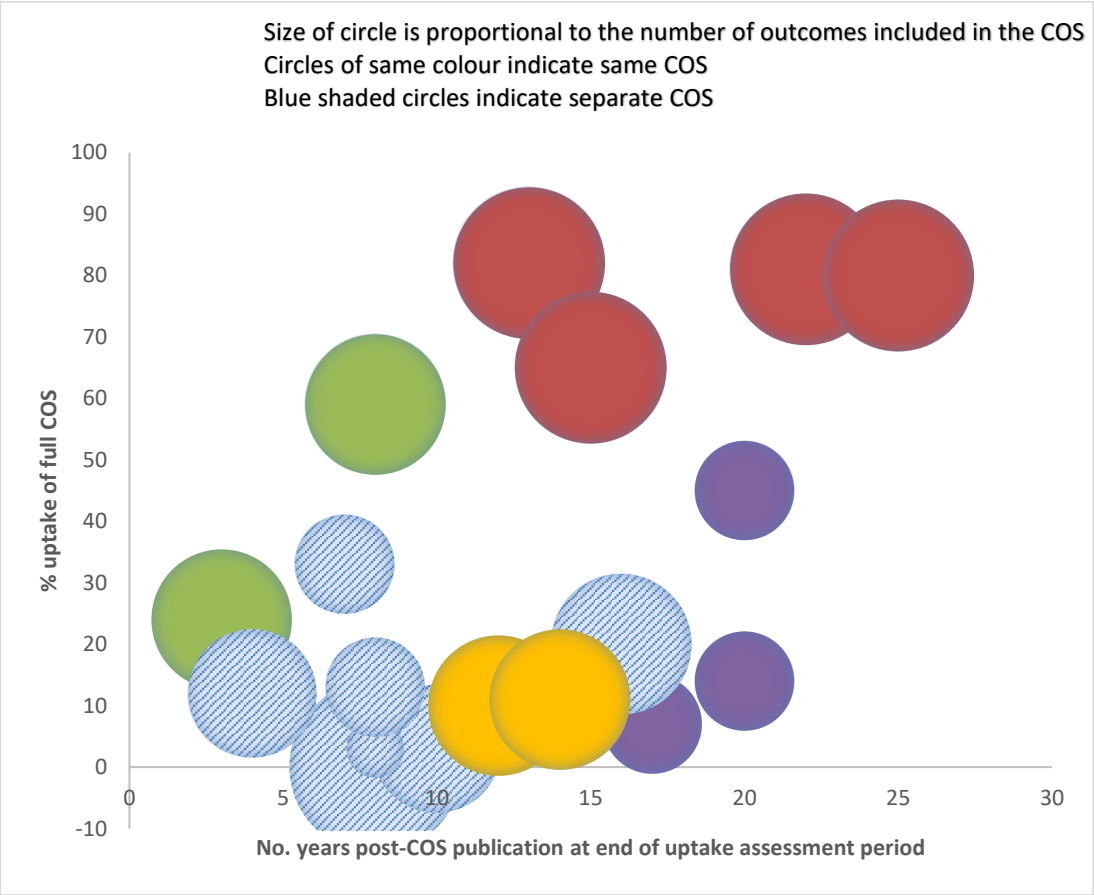
2.4.3 Methods used to assess uptake

Seventeen (65%) studies identified the RCTs or systematic reviews that they would assess by carrying out a systematic literature review (58-74). They extracted data about the outcomes included from the RCT reports and systematic reviews. Two (8%) studies searched systematic reviews to identify RCTs (75, 76) and one (4%) study included RCTs identified from one systematic review (77). Five (19%) studies identified RCTs by searching a clinical trials registry (78-82). One (4%) study identified RCTs through the citations received by the COS that they assessed and estimated the total number of RCTs as a denominator (83). Twenty-one studies (81%) reviewed outcomes measured by their selected RCTs or systematic reviews before the COS was published, or from the year of publication, as well as after. For those that only assessed the outcomes measured after publication of the COS, the COS had been published for at least three years before the start of the uptake assessment period.

2.4.4 Uptake of the COS in full by RCTs and systematic reviews

Seventeen studies reported the proportion of RCTs that measured the full set of outcomes recommended by a COS and one study reported this for systematic reviews (Table 1). For four of the eight remaining studies, uptake assessment was not their main aim and the other four studies did not indicate why they had not assessed uptake of the complete COS. For RCTs, the lowest rate of uptake reported was 0% (chronic gout) and the highest 82% (rheumatoid arthritis), and 10% uptake was found by the study assessing systematic reviews (chronic pain). Eleven of the COS had at least one study assessing uptake of the COS in full and for eight of these (73%), at least one such study reported that a maximum of 20% or less of the RCTs or systematic reviews assessed had measured the full COS. The assessed COS had recommended between one and 19 outcomes (Table 1). The COS with the least number of outcomes (n=1) had an uptake rate of 3% of RCTs measuring the full COS. No RCT measured the full COS with the highest number of outcomes (n=19), implicit from the fact that some of the outcomes were not measured in any RCT. The COS with the highest level of uptake recommended seven outcomes (plus one extra outcome for RCTs lasting more than one year) (Figure 5).

Figure 5: Uptake of full COS in RCTs and systematic reviews



2.4.5 Uptake of individual outcomes in the COS by RCTs and systematic reviews

Nineteen studies of RCTs reported the uptake of each outcome recommended by the COS, as did both studies of systematic reviews (Table 1). The results showed wide variation in the uptake rate for the individual outcomes in each COS. For example, one of those studies, assessing uptake of a COS for chronic pain, found that one outcome (pain) was included in 99% of trials while another (interpersonal functioning) was included in only 7% (68). The authors of five studies suggested that a review of the COS may be needed to address this and one study planned to use its findings to update the COS, which was for psoriatic arthritis (59). Six outcomes out of a total of 133 across all studies of uptake in RCTs were reported by 100% of RCTs and two of the six were from the same COS. None of the RCTs in one study for chronic gout measured three of the outcomes in the COS (which had nine COS outcomes in total) and none of the RCTs in a study for chronic pain measured 5 of the outcomes in the COS (19 outcomes in total).

2.4.6 Suggested barriers to uptake of COS

One of the studies investigated reasons for lack of uptake with the trialists directly (75) and reported that the majority of trialists not measuring the full COS were not aware of it when designing their trial. A further 15 studies suggested potential barriers that may have resulted in low uptake of the COS (Table 2). The absence of validated measurement instruments, or no consensus on which instruments should be used to assess the outcomes, was noted in four studies (58, 72, 73, 76). Six studies referred to limited patient or other key stakeholder involvement in the development of the COS as a potential barrier to uptake. Other barriers suggested were poor understanding of COS amongst trialists, lack of clarity, patient burden, cost and lack of standardised recommendations across regulatory agencies.

Table 2: Suggested barriers to uptake of COS

Reason for low uptake	Number (%) of studies mentioning this reason	Example
Lack of awareness	5 (19)	"This appears to be associated with the lack of awareness of the researchers regarding the existence of this standardized set of outcomes."[A21]
Lack of validated measurement instruments/no consensus on instruments	4 (15)	"There may also be applicability issues due to a lack of consensus regarding instruments to assess each domain."[A4]
Lack of patient involvement	4 (15)	"Further work is needed to obtain a better insight into what is relevant to the patient…"[A2]
Limited stakeholder involvement	2 (8)	"…the limited stakeholder involvement in the development of the hip fracture core outcome set may undermine its fitness for purpose."[A24]
Poor understanding of COS	2 (8)	"…authors may not understand the purpose of core sets…"[A7]
Lack of clarity	1 (4)	"Precise definition of PsA Core Domains is necessary…"[A13]
Patient burden	1 (4)	"Patients, for instance, may experience the requirement to complete these measures as an onerous burden…"[A10]
Cost	1 (4)	"Previous research suggests some trialists do not measure damage as it is costly to measure and requires further expenditure to obtain valid readings of radiographs"[A22]
Lack of standardised recommendations across regulatory agencies	1 (4)	"Some of this discordance may account for lack of uptake, and therefore future work may be undertaken to standardize recommendations across regulatory authorities." [A23]

[A] corresponds to uptake study listed in Appendix 4

2.5 Discussion

2.5.1 Main findings

There are currently few studies of COS uptake. The studies we identified covered five disease categories with just over half of the uptake assessments being carried out for COS that had been developed for rheumatic diseases. Rheumatology has the second highest number of published COS and another two of the five disease categories with the most published COS (neurology and orthopaedics and trauma) had at least one study assessing uptake of COS in its area (27). We did not find any studies assessing the uptake of COS for cancer, which has the highest number of COS of all disease categories (27). For the remaining 25 disease categories that have at least one published COS, we did not find an assessment of uptake of any COS in these categories.

The studies included in the review used various methods to assess uptake of COS. Most examined reports of RCTs that they had identified by reviewing the literature or searching systematic reviews. Not only are these lengthy processes, the information about the outcomes measured is not current as the outcomes would likely have been chosen some years before the trial reports were published. One study identified RCTs from the citations received by the COS publication. However, in our study of citation analysis as a method for COS uptake assessment, reported in Chapter 3, we found that not all RCTs using a COS cite the COS publication (84). A third method used, which removes the need to examine the report of the RCT and provides up to date information about the outcomes being measured, involved extracting information about outcomes from a trial registry. One of the uptake studies assessing a rheumatoid arthritis COS (78) tested this approach using ClinicalTrials.gov. The authors concluded that the uptake rate obtained by using information listed in the registry alone (77%) was an acceptable estimate of the uptake rate found by identifying the RCTs on the registry and examining the results in the registry or report of the RCT (81%). This approach provides a more efficient method to assess uptake, which may encourage further assessments to be carried out.

The studies that found low uptake of COS observed a number of barriers that might have hampered their use:
(i) To address a lack of patient and other key stakeholder involvement, and the issue of relevance of outcomes in existing COS, it may be prudent to consider an update to the COS.

The importance of patient involvement in COS development is being recognised by developers of new COS, with 94% of ongoing COS developers who responded to a 2017 survey stating that they had included patient participants (85). Whilst patient involvement may not in itself affect COS uptake, the relevance of COS will be improved with input from patient representation. Involving a range of key stakeholders when developing COS in addition to patients, for example, healthcare professionals, researchers and those who might use the COS, may further improve the relevance of the outcomes selected for inclusion.

(ii) To tackle uncertainty around outcome measurement instruments COS developers should focus on determining how to measure the outcomes in the COS once consensus has been reached on what to measure. The COMET and COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) Initiatives have developed guidance on selecting measurement instruments for COS to aid developers in this process (86).

(iii) We did not observe any relationship between the number of outcomes recommended by a COS and its rate of uptake. However, in a survey about uptake of the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (PedIMMPACT) COS for pediatric acute and chronic pain, some authors of systematic reviews felt that the six outcomes in the COS was too many (87). It is possible, however, that it is the perceived burden on patients to complete the outcome measurement instruments that lead to reluctance to implement them, as noted by Mulla et al. in their study of uptake of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) COS for chronic pain (68). COS developers may consider restricting the outcomes that are deemed to be core to a certain number, but in doing so need to consider the risk of missing a critical measurement from the core set. COS developers should bear in mind the burden on both patients and healthcare professionals when considering outcomes and their measurement instruments.

Several studies compared use of the outcomes that the COS recommended before and after publication of the COS (64, 66, 76). Only one of these studies, which assessed a COS for ankylosing spondylitis, noted some increase in uptake of the full COS after publication (0% RCTs before versus 20% RCTs after). The survey investigating uptake of the PedIMMPACT COS found a lack of awareness of the COS, with only a third of authors of RCTs and systematic reviews who completed the survey being aware of the COS (87). Lack of awareness was cited

as an issue by a report of a similar survey for the IMMPACT COS for chronic pain (88). The surveys also found that responders indicated that a lack of information about COS, lack of resources and time needed to use the COS, and in the case of systematic reviewers, the failure of RCTs to measure the COS outcomes, would affect use of the COS. Difficulty in implementing the outcomes due to them being complicated was also noted.

As described in Chapter 1, various strategies have been put in place to raise awareness of COS and encourage uptake. A set of minimum standards for COS development, COS-STAD (19), has been published to guide COS developers in producing high quality COS and to give trialists considering a COS a benchmark against which to assess its quality. To improve accessibility to COS, the COMET Initiative's database provides a freely accessible resource that collates all COS publications and allows researchers to identify potentially relevant COS for their study.

Overall, the studies that had assessed uptake of a COS in full found low levels of uptake. However, the standout exceptions to this were studies assessing uptake of the World Health Organisation (WHO) and International League of Associations for Rheumatology (ILAR) COS for rheumatoid arthritis (63, 75, 78, 79). The four studies assessing this COS show consistently high levels of uptake from 60-70% of RCTs measuring the full COS in one study, to 82% of RCTs in another. In their 2013 assessment of the rheumatoid arthritis COS (75), Kirkham et al. suggested that this may be attributed in part to the endorsement of the COS by the Food and Drug Administration (FDA) in 1996 and European Medicines Agency (EMA) in 1998, after which they observed an increase in uptake. In Kirkham's subsequent review in 2017 (78), it is noted that over 80% of RCTs assessed received commercial funding and so would have followed EMA/FDA guidance, including about the COS. In their third update of this work in 2019 (79) the authors found that industry funded trials were more likely to measure the COS. This might suggest that endorsement by drug regulatory authorities improves the uptake of COS in RCTs. In contrast, a study, that not only found a lower rate of uptake (45%) for the Knee, Hip and Hand Osteoarthritis COS, also reported a decrease in its uptake over time, and noted some inconsistency in recommendations across regulators, which may have impacted on the uptake of the COS (80).

2.5.2 Strengths and limitations

With increased awareness of the need for COS and greater endorsement by influential organisations, we expect there to be more studies assessing COS uptake in the future. This review will serve as a baseline for tracking uptake going forward.

We identified studies of COS uptake from the citation reports of COS publications. A limitation of the study is that it is possible that there are studies of uptake that did not cite the COS that they were assessing and these would not have been identified in the search, however we consider this to be unlikely.

2.5.3 Summary and next steps

To date, few studies have assessed uptake of COS in RCTs and systematic reviews and further work is needed to assess this across a wider range of health and COS areas and to understand the barriers and facilitators for uptake.

As the review found that uptake was low for some COS and health areas, it is important to investigate interventions that might improve COS uptake. Chapter 4 of this thesis investigates whether funders of RCTs can have an impact on uptake by recommending to their applicants that COS be considered for inclusion in their studies. It is also important to understand the barriers and facilitators to uptake in order to recommend the most appropriate interventions to achieve uptake of COS. Chapter 5 presents a qualitative interview study that investigated the barriers and facilitators to uptake.

In the systematic review we found that resource-intensive methods had been used to assess uptake of COS. For example, the majority of studies assessing uptake had carried out a literature search to identify RCTs that may have used the COS and then examined each RCT report to determine whether or not the RCT had measured the COS. It is important to investigate methods that would be less resource-intensive to assess uptake of COS in order to encourage COS developers to monitor uptake. An approach that had the potential to be more efficient in assessing uptake was citation analysis. Chapter 3 presents an exploration of citation analysis as an approach to assessing uptake of COS.

Chapter 3: An investigation of citation analysis as an approach to assess core outcome set uptake

Preface

Chapter 3 presents an investigation to determine whether the citations received by COS publications can be taken as an indicator of the level of uptake of the COS, thus providing an efficient method to assess uptake. Work arising from this chapter has been published in the Journal of Clinical Epidemiology (84) (Appendix 1) and sections of this chapter have been taken directly from the published manuscript. Karen Hughes carried out the data collection and analysis and wrote the original draft of the manuscript, which was edited by senior authors and has been subject to peer review.

3.1 Background

As described in Chapter 2, previous work has assessed the uptake of COS by examining RCT reports included in systematic reviews, or identified through literature searches, to establish whether the outcomes in the COS were measured in the RCTs (58-77). This method has proved to be resource-intensive. One study of uptake used citations of the COS publication to identify reports of RCTs that may have measured the COS (83). As with other previous work, this study then examined each individual RCT report to assess uptake of the COS making this as lengthy a method. However, citation analysis has the potential to provide an efficient method for COS uptake assessment if the number of citations received by a COS publication alone could be taken as an indicator of the uptake of the COS, thus avoiding the need to review the reports. Having a more efficient method to assess COS uptake could encourage COS developers to carry out their own assessments of uptake and if necessary take action to improve uptake where it is found to be low.

3.1.1 Citation analysis

In any scientific article an author will acknowledge the work of others by providing a reference to their publications. The publications referenced receive this acknowledgement in the form of a citation (89). Data gathered about the citations that a publication receives can provide a useful source of information for researchers, academic promotion boards and funding bodies.

Citation analysis is a method used to examine the citations found in a range of publications. This method involves counting the number of citations received by a publication or author and taking this figure as a surrogate measure of impact (90), i.e. the higher the citation count, the greater the impact. The results from this type of analysis may be used to inform the decisions of academic promotion panels or funding bodies by providing an indication as to the impact of an individual scientist's research (91). Citation analysis can also assist researchers in identifying the most notable work in their field from the vast amount available to them (92).

Citation analysis has the potential to provide an efficient method to assess the uptake of COS if the number of citations received by a COS publication could be reasonably taken as a surrogate measure of its uptake in RCTs.

3.1.2 Suitability of citation analysis for COS uptake

Before investigating citation analysis as a method to assess the uptake of COS, it is important to note the limitations that have been put forward in relation to citation analysis more generally and consider how they might influence the assessment of COS uptake.

Whilst it is likely that a highly cited publication received those citations because the work it reports is considered to be of a high standard, as Cater (93) pointed out publications are rarely cited for negative reasons, there are a number of other reasons that one author may cite another. For example, an author may be cited based on their reputation rather than the scientific merit of their work (89) or an author may show bias towards the work of colleagues (94). It is therefore not possible to make assumptions as to the quality of a COS solely based on whether its publication has received a high or low number of citations. For the purposes of COS uptake assessment, a citation should not be considered as a measure of quality (95).

Unless a specific request is made to exclude them, citation reports will contain self-citations. A self-citation occurs when an author refers to their own publications (96). Whilst it could be argued that self-citations should not be included in an author's citation rate, as it allows the author the opportunity to enhance their own citation rate, they should be included in a citation report assessing COS uptake. It is reasonable to expect that a COS developer should want to implement their COS in any RCTs where they are an investigator. However, it remains

important to consider the number of self-citations when examining the number of RCTs identified by citation analysis that had implemented a COS. If a high proportion of the RCTs implementing the COS were self-citations, uptake of the COS may not be as widespread as indicated.

Following the publication of an article it can take a number of years before it begins to accumulate citations. Typically, an article's citation rate only begins to increase significantly one or two years after it has been published and it can take a further three to five years to reach its maximum citation rate (90). Therefore, when using citation rate as a surrogate measure of COS uptake it is necessary to select COS publications that have been allowed sufficient time since publication to reach their maximum citation rate. COS that have been published in more recent years should not be assessed in this way.

3.2 Aims

The aim of this study was to examine the reliability of using citation analysis as a method of measuring COS uptake. Citation analysis has the potential to provide an efficient method to assess the uptake of a COS if the number of citations received by a COS report could be reasonably taken as a surrogate measure of its uptake by trialists.

3.3 Methods

3.3.1 Selection of a citation analysis tool

For this study, we selected Scopus as the citation analysis tool. This is in keeping with a review of Scopus, Web of Science and Google Scholar for citation analysis, which found that Scopus includes a wider range of journals and, in a search for a specific publication, Scopus retrieved 20% more citing articles than Web of Science. It was reported that the accuracy of Google Scholar was inconsistent (57).

3.3.2 Identification of COS reports

Of the 250 COS reports identified in the original COMET systematic review (23), 173 reports, those published in 2009 and earlier, were considered for the citation analysis. This cut point was chosen to allow sufficient time for trialists to become aware of the COS, implement it in their study and cite the COS report in the report of their RCT by the time of the analysis.

3.3.3 Selection of COS for citation analysis

Four COS were initially selected to evaluate the suitability of citation analysis for COS uptake assessment. Each COS provided a different aspect of interest to be investigated. A fifth COS was subsequently added to investigate a hypothesis suggested by the first round of evaluation. Appendix 5 details the characteristics of each COS.

3.3.3.1 Systemic sclerosis

Systemic sclerosis was selected as a test case to assess the methods to be used for citation analysis and the identification of RCTs from the citations retrieved. There are just two COS reports for this condition (97, 98), neither of which are highly cited, and so the full process could be trialled from start to finish relatively quickly. One of the COS reports focused specifically on outcomes while the other considered outcomes along with other RCT design issues.

3.3.3.2 Rheumatoid arthritis

Rheumatoid arthritis was selected as this health condition has one of the most recognised COS that was first published in 1993 following the 1992 OMERACT conference. The COS is reported in seven publications (50, 99-104) all of which were included in the analysis, along with three other publications reporting earlier suggestions of COS for the condition (105-107). All ten of the COS publications focussed specifically on recommendations for outcomes.

Another reason for the selection of rheumatoid arthritis was that the uptake of the OMERACT COS has been previously assessed by examining RCT reports included in Cochrane Reviews (75) to determine whether the outcomes in the COS had been measured. We wanted to establish how many of the RCT reports that the previous study had found to have measured the COS would have been retrieved using citation analysis. If only a proportion of these RCT reports were retrieved this would suggest that not all RCTs measuring a COS cite a COS publication in their RCT report thus bringing into question the scope of citation analysis in identifying RCTs that had measured a COS.

3.3.3.3 Eczema

Eczema was selected as this condition has a well-known COS due to a collaborative group working specifically on the agreement of COS in dermatological conditions, CSG-COUSIN (108) which is linked to the Cochrane Skin Group. One report relating to the development of a COS for eczema was published before 2009 and its focus was on recommendations for outcome measurement instruments. The report identified 20 instruments and recommended that only three of these should be used for future studies. We assessed the uptake of the study's recommendations (109).

3.3.3.4 Sepsis and critical care

Sepsis and critical care was selected as there are two associated COS reports, one of which specifically focused on the selection and measurement of outcomes (110) while the other considered outcomes whilst addressing other RCT design issues (111). As with the systemic sclerosis example, identifying the difference in citations of these two COS reports may offer some insight into which type of publication is more likely to be accessed and to have its recommendations implemented by trialists.

3.3.3.5 Female sexual dysfunction

Following analysis of the first four COS, female sexual dysfunction was added to the evaluation to further investigate the level of citation of a COS report that included recommendations for outcomes alongside recommendations for other RCT design issues (112).

3.3.4 Process

3.3.4.1 Citation analysis

Publications that cited at least one of the COS reports were identified using Scopus and the references to these publications were exported into Microsoft Excel. Duplicate entries of the same reference, caused by a publication citing more than one COS report, were removed to ensure that a reference to a COS report was not counted more than once. A publication relating to rheumatoid arthritis that had cited both the Felson 1993 (99) and Boers 1994 (102) COS reports, for example, would count as one citation for the COS.

3.3.4.2 Identifying RCTs

Cochrane Central Register of Controlled Trials (CENTRAL) (http://www.cochranelibrary.com/) was used as a tool to identify which of the citing publications were reports of RCTs. CENTRAL provides access to reports of randomised and quasi-randomised controlled trials obtained from a variety of published and unpublished sources. Keywords, such as condition, intervention and patient population, from the title of each citing publication were searched under the 'record title' option in CENTRAL. Because CENTRAL contains publications other than RCT reports, for example, systematic reviews, the abstracts of the articles identified by CENTRAL were screened to verify whether they were reports of RCTs. The full papers of those identified as RCT reports following the abstract check were obtained for further investigation into why the COS report was cited and whether the outcomes in the COS were measured, to determine whether the citations received by a COS report could be reasonably attributed to RCTs measuring the COS. To confirm the eligibility of RCT reports being included in the study, and the assessment of outcomes included in the RCT by the reviewer (Karen Hughes), the reports identified for rheumatoid arthritis were cross-checked with those identified in the previous rheumatoid arthritis uptake study. In cases where the same reports were identified the outcomes deemed to be measured by the RCTs were compared and there was 100% agreement between the findings of this and the previous study.

3.4 Results

3.4.1 Identifying RCT reports from the citations

For each of the disease areas, the search of CENTRAL enabled publications listed in the citation report that were not reports of RCTs to be removed. The accuracy with which CENTRAL identified RCTs varied between disease areas (Table 3). CENTRAL was least accurate in identifying rheumatoid arthritis RCTs, with 126 (53%) of the 236 publications identified by CENTRAL confirmed as reports of RCTs. It was most accurate for eczema, with six (86%) of the seven records identified being confirmed as RCT reports when the abstracts had been screened manually.

Table 3: Figures from citation analysis for each disease area

Disease name	Type of publication	No. of citations for COS reports	No. of citations identified as possible trials (CENTRAL)	No. of citations confirmed as trials (abstract check)	No. (%) of trials measuring all outcomes in COS	% of citations from trials
Systemic sclerosis	COS-only	27	1	0	0 (0%)	0%
	General design	97	15	10	0 (0%)	10%
Rheumatoid arthritis	COS-only	1472	236	126	98 (78%)	9%
Eczema	COS-only	136	7	6	6 (100%)	4%
Sepsis and critical care	COS-only	64	4	4	1 (25%)	6%
	General design	711	23	13	0 (0%)	2%
Female sexual dysfunction	General design	723	40	23	6 (26%)	3%

3.4.2 Number of RCTs identified that measured the COS

Not all of the citing publications that were identified as RCTs measured the recommended COS (Table 3). For three of the disease areas (systemic sclerosis, sepsis and critical care and female sexual dysfunction), less than a third of the RCTs citing a COS report measured all the recommended outcomes. None of the ten RCTs citing the report on general RCT design issues for systemic sclerosis measured the COS, 25% of the four RCTs citing the COS-only report and none of the 13 RCTs citing the general RCT design issues report for sepsis and critical care measured the COS and 26% of the 23 RCTs citing the general RCT design issues report for female sexual dysfunction measured the COS. In contrast, 78% of the 126 RCTs citing a COS-only report for rheumatoid arthritis measured all the outcomes in the COS and all 6 RCTs citing the outcomes-only report for eczema followed its recommendations on outcomes.

Assessment of a random sample of RCT reports that had cited a COS report but did not measure all the recommended outcomes (a maximum of five reports for each condition and type of COS report, where available) identified a variety of reasons for citing the COS report (Table 4). Few of the RCTs were citing the COS report in relation to outcomes. The majority

were referencing recommendations about other RCT design issues that had been addressed in the COS report, for example, patient inclusion criteria, or definition of a disease or disorder. Some of the RCTs referencing a COS report that had focussed only on outcomes had measured some of the COS outcomes, and cited the report for this reason, but did not provide an explanation for not measuring all of the recommended outcomes.

Table 4: Reasons that trials not measuring the COS cited COS reports

Disease area	Reason for citing COS report
Systemic sclerosis (general RCT design issues report)[*1]	Acknowledging that clinical trials are recognised to be difficult in the disease area
	Patient inclusion criteria (2 trials)
	Patient population
	Determination of disease onset
Rheumatoid arthritis (COS-only reports)	Acknowledged COS but limited the number of outcomes to three that could be obtained by self-assessment by the patients
	The patient's global status and level of overall pain and the physician's global assessment were scored on a visual-analogue scale.
	Measured the core set of measures apart from radiographs in trial lasting more than one year. The trialists acknowledged that this should be done in future trials.
	The variables chosen included 4 of 7 measures proposed for assessing disease activity by the ACR in 1993.
	Problems with outcomes have been addressed with the development of a COS
Sepsis and critical care (COS-only report)[*2]	Named some of the proposed COS outcomes
	Inflammatory markers can provide additional support for a phase III study
	Sensitivity of organ dysfunction scales
Sepsis and critical care (general RCT design issues report)	Definition of sepsis (4 trials)
	Patient inclusion criteria
Female sexual dysfunction (general RCT design issues report)	Definition of female sexual arousal disorder (3 trials)
	Definition of hypoactive sexual desire disorder (2 trials)

[*1] There were no citing trials for the systemic sclerosis COS-only report so no sample available

[*2] Three citing trials were available for the sepsis and critical care COS-only report that did not measure the COS

3.4.3 Type of COS report cited in RCT reports

For disease areas where two types of COS report exist, i.e. reports focusing only on outcomes and reports considering outcomes whilst addressing other RCT design issues, the general design issue reports received more citations from RCTs (systemic sclerosis n=10, sepsis and critical care n=13) than the outcomes specific reports (systemic sclerosis n=0, sepsis and critical care n=4). However, none of the RCTs citing the general design issues papers measured the outcomes recommended. While the COS-only reports for these disease areas also had a low number of citing RCTs measuring the COS (systemic sclerosis n=0, sepsis and critical care n=1), in cases where there was only one type of report, the outcome specific reports had considerably more citing RCTs that had followed their recommendations (rheumatoid arthritis 78%, eczema 100%) than a general design issues report (female sexual dysfunction 26%) (Table 3).

3.4.4 Comparison of methods of uptake assessment for rheumatoid arthritis trials

A previous study that examined RCT reports included in Cochrane Reviews to assess uptake of the OMERACT COS (75) found that 100 of the 350 RCTs that were identified measured all the outcomes in the COS. When the 350 RCT reports were cross-referenced with those in the citation report, it was found that only 25 of these 350 RCTs had actually cited a COS report (Table 5). Therefore, for this particular sample of RCTs, citation analysis returned an uptake figure of 25 out of 350 RCTs, whereas 100 of these 350 RCTs had actually measured the outcomes in the COS. Further comparison of the RCTs shows that 20 of the 25 identified by citation analysis measured the outcomes in the COS.

Table 5: Comparison of uptake for 350 rheumatoid arthritis trials identified in Cochrane Reviews

	Cochrane reviews method	Citation analysis method
No. of trials identified	350	25
No. (%) of trials that measured the COS	100 (29%)	20 (6%)

3.4.5 Citations received from publications other than trial reports

For each of the disease areas we assessed, a large proportion of the citations received by the COS reports were from publications reporting on something other than RCTs (Table 3). For

both types of COS report in all of the disease areas, at least 90% of the citations were not from reports of RCTs.

3.5 Discussion

3.5.1 Main findings

The aim of this study was to evaluate whether citation analysis would provide an efficient method to assess COS uptake. While we have been able to demonstrate that citation data can be readily accessed, further investigation shows that it is not possible to assume that the citations received by COS reports are from RCTs measuring the COS they recommend. For example, of the 775 citations received by the sepsis and critical care COS reports, only 17 were from RCTs and of these 17 RCTs just one measured the COS recommended by the report they had cited. These figures demonstrate first that COS reports are not only cited in RCT reports but also in other types of publications and secondly that an RCT report may cite a COS report for reasons other than adopting the COS, for example, other aspects addressed in the COS report such as patient inclusion criteria and definition of a disease. Therefore, it is not possible to use the number of citations received by a COS report alone as a surrogate measure for uptake of the COS by RCTs. Additional steps are required to generate an indication of uptake, as discussed below.

Further assessment of each citing publication was needed to establish whether it is an RCT report and using CENTRAL to determine this can be a lengthy process. Key words from each publication title needed to be manually input and in cases such as the rheumatoid arthritis example, which has 1472 records, this was time consuming. As it is evident that CENTRAL contains publications other than RCT reports, it is necessary to conduct further screening of abstracts to verify those publications identified in CENTRAL. The accuracy of CENTRAL to identify RCTs relies in part on the input of individual Cochrane Review Groups and it is evident that there are differences in the maintenance of records and therefore the accuracy of CENTRAL between disease areas.

When all citing RCTs have been identified, an assessment of the RCT report is needed to determine whether all the outcomes in the recommended COS were measured, adding a further time consuming stage to the process as with other previous methods.

A study assessing uptake of The Prevention of Falls Network Europe (ProFaNE) COS for fall injury prevention (83) used citation analysis to identify RCTs citing the report of the COS. Similar to the disease areas reported here, a small proportion of the citations received by the COS report were from RCTs, with 34 RCTs found in 464 citations. The 34 RCTs were identified by screening the citing articles' titles and abstracts and excluding reports that were protocols, pilot studies or secondary reports of an RCT already extracted. The majority of citing articles were observational studies (46%), editorials or reviews (23%) or methodological articles (13%). Analysis of the RCT reports found that the majority of RCTs referred to the COS report in relation to other recommended methodology, for example, length of follow up period, rather than outcomes. This finding is echoed in the study reported here, where COS reports are often referenced for design issues that had been addressed in addition to outcomes. Analysis of the ProFaNE COS also found that, while most RCTs had reported at least one of the recommended core outcomes, only one RCT had reported on all core outcomes.

The results of the ProFaNE COS study support the finding that the number of citations received by a COS report cannot be taken as an indicator of its uptake and that further analysis is needed to ascertain whether the citing articles are RCTs measuring the COS. The number of steps and the amount of time needed to complete this process means that citation analysis is no more efficient for uptake assessment than the method of examining RCT reports used previously (64, 68, 75). Rather, citation analysis provides an alternative method of identifying RCT reports that can then be assessed. Both citation analysis studies highlight that COS reports are mostly cited in articles that are not RCT reports and it would be of interest to further investigate the types of articles citing COS reports and their reasons for doing so.

In addition to these findings, there are additional limitations of citation analysis for COS uptake assessment that should be noted.

Citation analysis does not consider those RCTs that did measure the outcomes in a COS but did not cite a COS report thus affecting the accuracy of citation analysis as an indicator of uptake. As demonstrated by the comparison of methods to assess uptake of the rheumatoid arthritis COS, not all RCTs that measure a COS cite a COS report. This would lead to the rate of COS uptake being underestimated by citation analysis. In the case of the rheumatoid

arthritis COS, a study previously demonstrated that 100 RCTs from a particular sample of 350 measured the COS (75). However, when we cross referenced this same sample with the citation report, only 20 of the RCTs that had measured the COS were present, plus a further five from the sample that had not measured the COS. Identifying a sample of RCTs and taking the number that had cited a COS report as a surrogate measure of COS uptake would remove the time consuming process of examining the full RCT report. However, this rheumatoid arthritis example demonstrates that uptake rate assessed in this way could be greatly underestimated.

A further limitation of citation analysis for COS uptake is the absence of data on the number of RCTs that were conducted in the relevant health condition for the time period being investigated. To make an accurate assessment of uptake it is necessary to know the proportion of the total number of RCTs that used the COS. Citation analysis can only retrieve information about RCTs that have cited a COS publication and does not provide the total number of RCTs conducted as a denominator.

Along with the evaluation of citation analysis as a method for assessing COS uptake, the findings raise an interesting hypothesis in relation to the effect that the focus of a COS report may have on COS uptake. Of the two COS reports for systemic sclerosis, one considered outcomes while addressing other RCT design issues (97) whereas the other focused specifically on the selection of outcomes (98). Table 4 shows that none of the citing RCTs cited the outcomes specific paper and although this might be expected as that COS report was published in 2008 and the latest RCT report identified was published in 2011, it generated a hypothesis that a COS recommended in a general RCT design publication is more likely to be implemented. However, further investigation shows that none of the RCTs citing the general RCT design paper measured the COS. They had cited the paper in relation to other design issues, for example, patient population and inclusion criteria, and not in relation to the choice of outcomes. Further investigation into the measurement of outcomes in a COS by RCTs that cited a general design issues publication for female sexual dysfunction revealed that 26% of RCTs citing the publication measured the COS. In contrast, 100% of RCTs that cited the eczema report and 78% of RCTs that cited a rheumatoid arthritis COS report, all of which focused specifically on the selection of outcomes, followed the report's recommendations on outcomes. It may be that when choice of outcomes is one of several issues addressed by a report, the recommendations relating to outcomes become lost in the

volume of information provided by the publication. Trialists looking specifically for advice on a particular area of RCT design may overlook the recommendations regarding outcomes in these reports. Although reports focussing only on choice of outcomes may not be as highly cited as those covering a wider range of issues, the trialists citing these reports may be more likely to follow the recommendations in relation to which outcomes to measure. This may suggest that a COS should be reported independently of other design issues to attract the most attention, but this hypothesis requires further investigation.

3.5.2 Summary and next steps

While citation data can be readily accessed, it should not be assumed that the citing of a COS report indicates that an RCT has measured the recommended COS. RCTs measuring the relevant COS made up a small proportion of the total number of citations for COS reports. Not all RCTs citing a COS report measured all the recommended outcomes. Some RCTs cited the COS reports for other reasons, including the definition of a condition or other RCT design issues addressed by the COS report. Alternative methods for assessing COS uptake are needed.

Following this study, and described in Chapter 2, further work was carried out by Kirkham et al (78) to find an efficient method to assess COS uptake. This involved extracting information about outcomes from a trial registry. When testing this method using a COS for rheumatoid arthritis, the authors found an uptake rate of 77% based on the information held in ClinicalTrials.gov which they concluded was an acceptable estimate of the uptake rate of 81% found by examining the reports of the RCTs. Furthermore, this method provides a more up to date assessment of COS uptake than assessing RCT reports that will have been published several years after the RCT design stage when outcomes were chosen.

It is hoped that this less resource-intense method will encourage more assessments of COS uptake. In cases where an assessment of COS uptake reveals limited use of the COS, it is necessary to propose strategies to improve uptake. Where strategies have already been suggested it is important to assess whether they are having the desired impact in increasing uptake. Chapter 4 presents an assessment of the impact that a funder of RCTs may have on COS uptake by recommending that their applicants consider using COS.

Chapter 4: An assessment of the impact of a funder's recommendation to use core outcome sets

Preface

Chapter 4 presents an assessment of the impact of a funder's recommendation to its applicants to consider using COS in their studies. Work arising from this chapter has been published in PLoS ONE (113) (Appendix 1) and sections of this chapter have been taken directly from the published manuscript. Karen Hughes carried out the data collection and analysis and wrote the original draft of the manuscript, which was edited by senior authors and has been subject to peer review.

4.1 Background

As described in the systematic review reported in Chapter 2, COS uptake by RCTs is limited. It is therefore important to look at interventions to improve uptake. One such intervention to encourage uptake of COS is for funders to recommend their use. In January 2012, the UK National Institute for Health Research Health Technology Assessment Programme added the following statement to its guidance for applicants for all RCT and evidence synthesis funding streams:

"Details should include justification of the use of outcome measures where a legitimate choice exists between alternatives.

- Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established."

4.1.1 The National Institute for Health Research Health Technology Assessment Programme

The National Institute for Health Research (NIHR) is funded by the Department of Health and Social Care and is the largest funder of health research in the UK. The NIHR funds research across ten programmes, including the Health Technology Assessment (HTA) programme (https://www.nihr.ac.uk/). The NIHR HTA programme funds primary research and evidence syntheses that address the needs of the NHS (114). The programme consists of the

researcher-led workstream which allows researchers to investigate topics that are within the programme's remit, and the commissioned workstream which calls for research on a specific question (https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm).

4.2 Aims

Building from the NIHR HTA's endorsement, we aimed to investigate its impact, by examining applications to the researcher-led stream of the NIHR HTA programme since 2012 to determine whether trialists followed the guidance to search for a COS using the COMET website, or some other source, and if so to find out how they used the information they found, or if not to find out how they chose the outcomes for their studies.

4.3 Methods

4.3.1 Accessing NIHR HTA funding applications for RCTs

The NIHR Evaluation, Trials and Studies Coordinating Centre, through the Research on Research programme, provided access to data extracted from the outcomes section of all NIHR HTA full primary research applications submitted to the researcher-led funding stream between January 2012 and December 2015 (n = 95). This included funded and non-funded applications and we were also given the detailed project description for each application.

4.3.2 Extracting the data

The outcomes section of each application form and detailed project descriptions were searched for information included about the COMET website, COS, or other justification of choice of outcomes for the RCT. The information was extracted and recorded in a matrix by Karen Hughes (KH) (Appendix 6). For each application KH also searched the COMET database to establish whether a COS existed at the time of submission, or whether a COS was available that may have been relevant to the application even if not an exact match. Where no COS existed at the time of application the COMET database was searched to determine whether a COS had since been developed. A sample of the database searches were checked for accuracy by Paula Williamson (PW) and Jamie Kirkham (JK) and any discrepancies were discussed until agreement was reached.

4.3.3 Survey of chief investigators

A survey was sent to all applicants by email via the NIHR Research on Research team, to further investigate the researcher's decision to search for and use a COS or not and to discover more about their strategies for selecting outcomes. The email contained a link to an online survey set up using SelectSurvey software (https://selectsurvey.net/). One of four versions of the survey was sent to each applicant depending on the information extracted from their application:

a) Survey 1 was sent to applicants who had mentioned the COMET website or COS and had found and used a COS that had been published or was in development.

b) Survey 2 was sent to applicants who had mentioned the COMET website or COS and had not found a relevant COS for their trial.

c) Survey 3 was sent to applicants who had not mentioned the COMET website or COS but had given reasons for their choice of outcomes.

d) Survey 4 was sent to applicants who had not mentioned the COMET website or COS and had not given reasons for their choice of outcomes.

Following the initial mailing follow up emails were sent to non-responders on three occasions. Applicants were asked about their use of the NIHR guidance when completing their application, their decision to search for and use a COS or not, including their assessment of the COS, and reasons for their choice of outcomes where a COS was not found or searched for. Appendix 7 contains copies of the questions in each of the four surveys.

Ethical approval for the survey was granted by the University of Liverpool Health and Life Sciences Committee on Research Ethics (Human participants, tissues and databases) on 29/08/2017 (reference 2215). Study information was included in the email sent to applicants with an explanation that completion of the survey would be taken as the applicant's consent to participate (Appendix 8).

4.4 Results

4.4.1 Applications with a COS at the time of submission

A search of the COMET database identified COS for 24 (25%) applications at the time that they were submitted. For three applications the search identified COS that, although not an exact fit, may have been relevant to the health condition in the application. Of the remaining

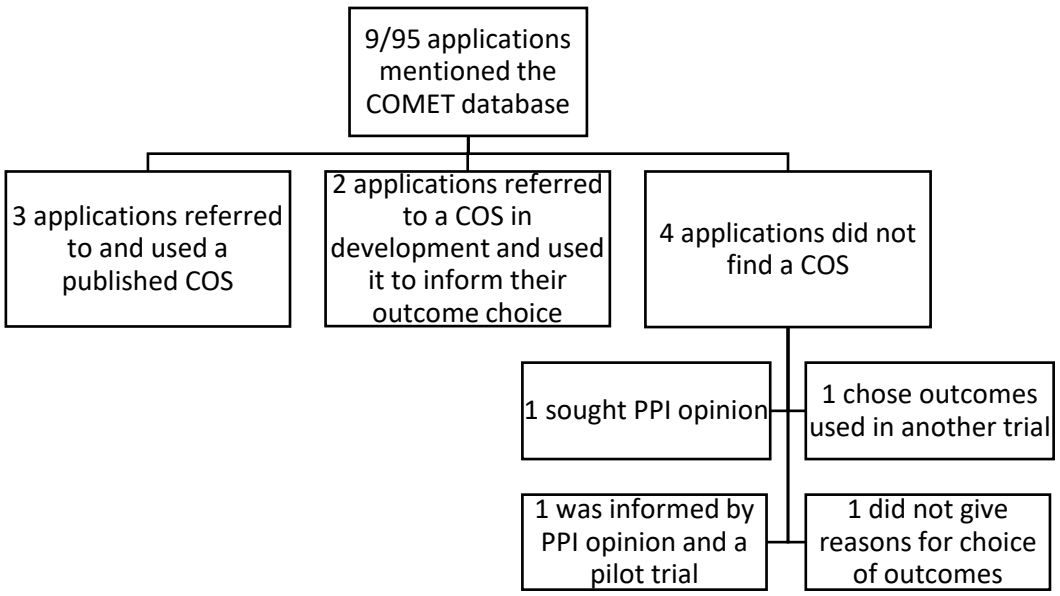
68 applications that did not have a COS relevant to their health condition at the time, 32 now have COS that have since been developed (as of October 2018).

4.4.2 Examination of application forms

4.4.2.1 Applicants searching the COMET database

Nine (10%) of the 95 applicants stated in their application that they had searched the COMET database. Three found a relevant published COS and proposed that it would be included in their study, two found a relevant COS that was in development and used the interim findings to inform their decision on which outcomes to include in their study, and four did not find a relevant COS (Figure 6). A search of the COMET database by one author (KH) identified that COS did exist for the conditions being studied in two of these four RCTs but the applicants stated that their search did not identify relevant COS. Although a COS did not exist for one of the four applications at the time of submission, a COS in development was registered on the COMET website, and for the fourth application there is no COS in the COMET database as of October 2018. Three of the four applicants who searched COMET but did not find a COS relevant to their study explained how they reached the decision about which outcomes to include in their RCT. Figure 6 shows that reasons given included the opinion of patients or the public, information from a pilot trial, and the use of outcomes that had been used in previous trials of the same health condition.

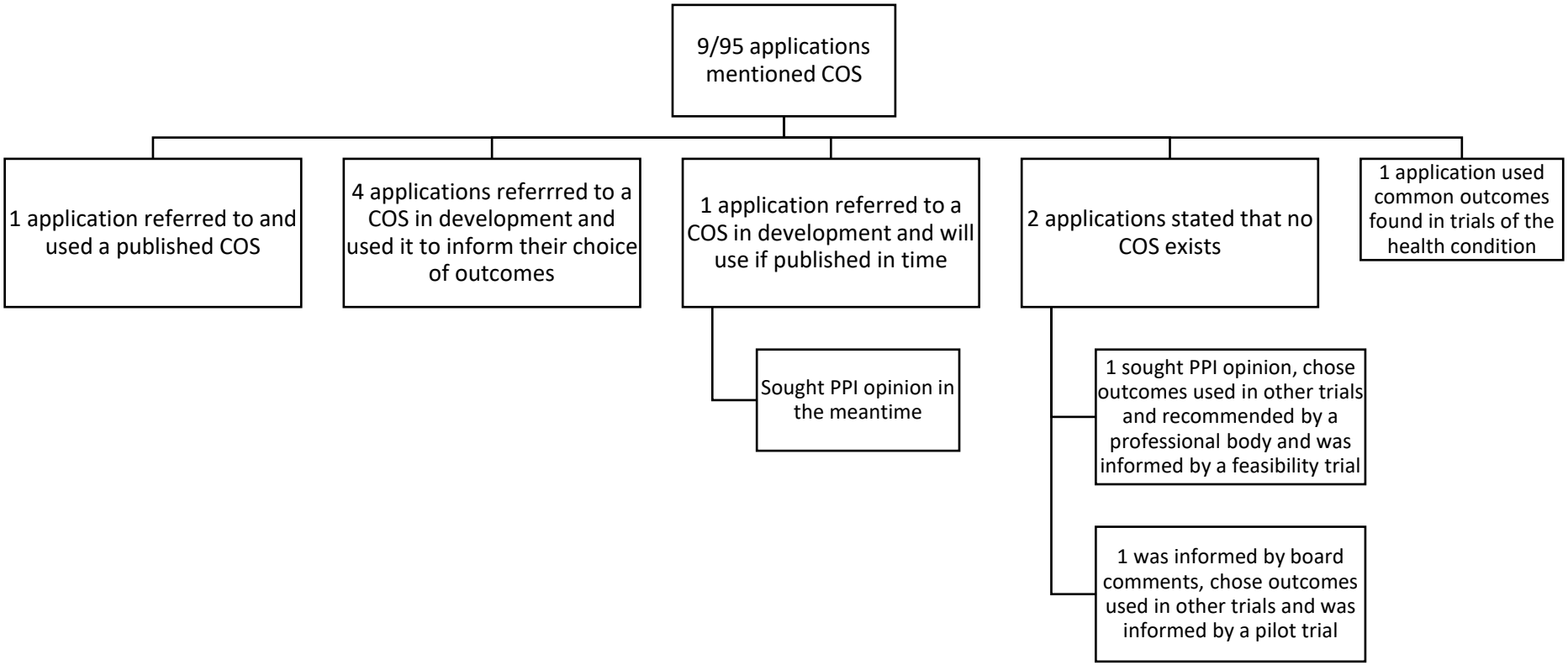
Figure 6: Applications that referred to a search of the COMET database for a COS



4.4.2.2 Applicants referring to a COS

Nine (10%) applicants mentioned COS in their application but did not make reference to the COMET database: one referred to a published COS that they intended to include in their study; five referred to a COS in development (with four of these using the COS to inform their choice of outcomes and the fifth stated that they would use the COS if it was published in time for their study but sought patient opinion in the meantime); two applicants stated that no relevant COS existed but did not explain the steps that they took to find this out; one applicant referred to core outcomes in terms of common outcomes used in RCTs of their health condition but a COS had not been developed (Figure 7). A search of the COMET database by KH confirmed that no relevant COS were recorded for the conditions of interest in the two RCTs that did not find a COS. These applicants used a combination of patient and public opinion, outcomes used in other RCTs and recommended by a professional body, funding board feedback, and information from a feasibility or pilot trial to inform their choice of outcomes in the absence of COS (Figure 7).

Figure 7: Applications that referred to a COS but did not refer to the COMET database



4.4.2.3 Sources of information accessed by trialists to inform their decision about the outcomes to include in their study

Of the remaining 77 applications that did not mention the COMET database or COS, 58 contained information about how the researchers chose the outcomes to include in their study and some common themes were apparent. Examples of the information extracted for each theme are presented in Table 6.

Patient and public opinion: Thirty one applicants (53%) described seeking the views of patients and the public with knowledge of the condition of interest on the outcomes that had been chosen, or asking for their opinion on which outcomes should be included in the study. In some cases, the researchers described changing or adding outcomes based on public and patient feedback.

Outcomes used in other trials: Twenty two applicants (38%) looked at outcomes used in previous RCTs to inform their choice. One reason given for this was to enable comparison between RCTs.

Recommendation from a professional body: Thirteen applicants (22%) sought information from a professional body associated with the health condition that was the subject of their RCT and included an outcome that had been recommended by the professional body.

Feedback from the funding board: Twelve applicants (21%) amended at least one of their outcomes following recommendations fed back from the funding board. This included adding outcomes not included in the preliminary application, reducing the number of outcomes included in the preliminary application, and in six of the 12 applications making changes to the primary outcome.

Information from a feasibility/pilot trial: Nine applicants (16%) used the results of a feasibility or pilot trial to inform their choice of outcomes. In three cases, the applicants amended their outcomes following the feasibility/pilot trial, for example, by reducing the number of outcomes to reduce patient burden and improve retention.

Practitioner opinion: Three applicants (5%) were explicit that they took on board the opinion of practitioners when selecting outcomes, referring to surveys of clinicians either published previously or conducted by the applicant.

Table 6: Examples of the sources applicants used to inform their choice of outcomes as extracted from the applications

Source	Number (%) of trials mentioning this source	Example
Patient and public opinion	31 (53%)	Feedback from parents led to changes in the outcome measures we will use . . .
Outcomes used in other trials	22 (38%)	We have selected this measure because of its . . . properties including . . ., and because it has been widely used in other randomised trials of . . . with . . .
Recommendation from a professional body	13 (22%)	The primary outcome measure is . . . (as recommended by the . . . Association for . . .)
Feedback from the funding board	12 (21%)	The outcomes have been amended taking into account the board's recommendation . . .
Information from a feasibility/pilot trial	9 (16%)	. . . and data from our pilot trial were used to inform choice of outcome measures and the sample size calculations.
Practitioner opinion	3 (5%)	. . . is the key outcome for clinicians.

4.4.2.4 Applications that did not include reasons for choice of outcomes

Twenty (21%) applicants did not explain how or why they chose the outcomes to include in their proposal. One of these applicants had searched for but did not find a COS and 19 did not state whether they had searched for a COS before choosing outcomes for their study.

4.4.3 Survey of chief investigators

Forty-seven of the 95 applicants (49%) submitted a fully completed survey.

4.4.3.1 Following the HTA guidance for applicants

All 47 applicants stated that they had referred to the NIHR HTA guidance for applicants when completing their application and ten of those 47 reported that they had followed the recommendation in the guidance to search the COMET database for a COS. Eight of these ten had not mentioned their search in their application, and of those eight, two found a relevant COS. Although they had referred to the guidance, a further eleven applicants stated that they did not search for a COS. Of the remaining 26 applicants, 19 reported that they had considered a COS using one or more resource other than the COMET database. Six considered a COS without a search of the COMET database as they were involved in the development of the COS, 12 carried out a search of the literature either as their only source of information or alongside other sources, seven applicants discussed the existence of COS with personal contacts and experts in the field, and it was not clear from seven applicant's responses if they searched for a COS before deciding on their outcomes (Table 7). Ten of these 19 applicants that searched for a COS had not mentioned this in their application and one of those 10 found a COS.

Table 7: Survey responses of 47 applicants about searching for a COS

	Searched COMET database	Involved in development of COS	Searched literature	Expert opinion	Did not search for a COS	Not clear if searched for a COS
No. of applicants*	10 (21%)	6 (13%)	12 (26%)	7 (15%)	11 (23%)	7 (15%)

* Some responders searched more than one source of information

4.4.3.2 Applicants' decisions to use a COS

Applicants who found and used a COS, either through a search of the COMET database or some other source, provided a number of reasons for deciding to use the COS. Applicants referred to the benefits of COS (e.g. enabling comparison of studies and including outcomes that had been peer reviewed), external influence (e.g. from a Clinical Trials Unit and journal), and being involved in the development of a COS. Table 8 shows examples of applicants' comments. Some applicants who found a COS that was relevant to the health condition in their study, even if not an exact fit for this, explained how they used the COS to inform their choice of outcomes. This included facilitating discussions of the applicants, experts and patient and public focus groups around which outcomes to choose, and incorporating some outcomes from the COS. In contrast, one applicant who found a COS that was relevant

explained how they chose not to use it and instead used their experience of conducting RCTs and researching outcomes in the relevant health area to inform their choice of outcomes.

Table 8: Examples of reasons given by applicants for their decision to use a COS

COS found and used	
Reason	**Example**
Benefits of using a COS	Essential to compare studies across the world Peer reviewed outcomes
External influence	Team in Clinical Trials Unit in . . . has been involved in the development of COS before and influenced my decision Journal publication requirements
Involved in the development of the COS	The COS for . . . was created from an . . . project - I was the lead investigator The lead author of the main COS publication was a co-applicant on the grant
Relevant COS informed choice of outcomes	
How	**Example**
Facilitated discussions about outcomes	Yes the COS was used in discussions of choice of outcomes We also discussed the proposed outcome measures at a PPI focus group. There was a great deal of discussion re the outcomes chosen with experts and PPI
Outcomes included in the trial	Core . . . outcomes incorporated Used the outcomes which were common in similar . . . research

4.4.3.3 Choice of outcomes by applicants not using a COS

Those applicants who responded to the survey and had already provided justification of choice of outcomes confirmed what they said in their applications. Additional information came from seven applicants who had not mentioned COMET or COS, or explained their choice of outcomes in their application. In the survey, these applicants echoed reasons given by others for their choice of outcomes, i.e. two were informed by a feasibility trial, six chose outcomes that had been used in other RCTs, five were informed by feedback from the funding board and three considered patient or public opinion.

4.5 Discussion

4.5.1 Main findings

This study set out to assess the impact of a funder's recommendation to clinical trialists to search for and use a COS in their study, and to discover how trialists choose outcomes to measure when a COS is not available. A number of trial funders endorse the use of COS and the COMET database (http://www.comet-initiative.org/cosuptake) and this study focused on the impact of the recommendation by the NIHR HTA programme.

The results suggest that a funding body has the potential to have an impact on COS uptake by encouraging trialists to search for a COS. Based on the information provided by applicants in their application forms, and answers to survey questions, it is evident that at least 17 of 95 applicants searched the COMET database and seven of those applicants found a published COS to use in their RCT or a COS in development to help inform their choice of outcomes. In addition, another 19 applicants searched for COS using other sources, for example, a literature search, and 6 of those applicants found a published COS or a COS in development to inform their study. Out of a possible 24 applications that could have included a completed, published COS, seven (29%) applications did so.

However, it is possible that more applicants may have searched for and included a COS in their application but it was not possible to determine this in the assessment of the applications. This is because not all NIHR HTA applicants mention their search for a COS in their application form. The survey of chief investigators identified 18 applicants who had searched for a COS using the COMET database or another source but had not mentioned this in their application. Therefore, there may be more steps that could be taken by funding bodies beyond making the recommendation about COS that could further encourage uptake, make it possible to accurately assess the full impact of the recommendations, and ascertain whether the guidance is being adhered to.

For example, if the NIHR staff conducted their own search they might identify COS that should have been considered by the applicant. It would be useful for the funding board to be notified of the results of such a search, but it is important to acknowledge that this would require extra resources for staff to carry out the checks. For some funders this additional process may prove to be too resource intensive. A possible solution that would eliminate the need for additional resources in these circumstances might be for a member of the funding

board to carry out a search of the COMET database during discussions about the outcomes included in the applications. It is evident from the application forms that 12 applicants in the cohort took advice about outcomes from the funding board and seven more applicants who had not mentioned this in their application forms reported having done so in the survey. If the board established whether a COS was available when discussing applications, they could recommend its uptake in the feedback provided to the applicant. The search for a COS using the COMET database is a relatively quick process where a disease category or name can be selected and results can be restricted to show relevant COS for RCTs. Although some applicants in the study used other ways to search for COS, e.g. by conducting their own search of the literature, the COMET database is recommended as it collates information about existing and developing COS in one place making it an effective resource for trialists. The content for the database comes from a systematic review (23) that is updated annually to ensure that the information held in the database is current (24-29).

As this study shows that some researchers are not explicit in their application about searching for COS, it may help to prompt them to report this by including a check list alongside the application form where the applicant can indicate what search they had done (e.g. of the COMET database). This would also provide further encouragement for applicants to search for a COS because although all survey responders stated that they used the guidance notes, eleven went on to report that they did not search for a COS. While it could result in extra burden for applicants to complete an additional checklist, some journals have demonstrated that introducing such processes is possible by incorporating reporting guidelines as recommended by the EQUATOR Network (http://www.equator-network.org/toolkits/using-guidelines-in-journals/). This may include a requirement for authors to follow reporting guidelines and complete a checklist to confirm which guideline they have used that can be checked by editorial staff or peer reviewers. An alternative approach would be to include the recommendation about COS in the outcomes section of the application form, as well as in the guidance to applicants, to act as a further prompt to applicants. This approach has been put into practice by KCE, the Belgian Health Care Knowledge Centre (https://kce.fgov.be/en/kce-trials-2018-investigator-led-call). If the recommendation to search for and use COS became common practice across all funders of RCTs, and the suggested processes for checking and further advising applicants were put in place, there would be great potential for funding bodies to have a significant impact on the uptake of COS in RCTs.

Along with funders it is recognised that recommendations from other sources, such as trials registries, could facilitate the uptake of COS (115). In addition, support from end users of COS, for example, clinical guideline organisations, HTA bodies and payers, may encourage uptake (116).

As well as the facilitators to COS uptake it is also important to consider the barriers. For example, one survey respondent in the study chose to use their team's experience in RCTs and outcomes research to select outcomes for their study rather than using a COS. It is key that trialists are invested in a COS for their condition of interest for uptake to be achieved (19). Without the investment of end users, the development of a COS is, as noted above, likely to result in research waste through poor uptake.

Although there are over 300 published COS available (29), there are still many conditions in need of a COS, and for 68 of the 95 applications assessed in this study a COS, or potentially relevant COS, did not exist at the time of submission. If those 68 applications were submitted at the later date of October 2018, 32 would find a COS that has since been developed. Although the gaps are being filled, if a COS has not been developed, researchers need to access other sources to inform their decision about which outcomes to include in their RCTs and identification of the sources they use might highlight opportunities for COS developers to improve access to their work and its output. For example, more than half the applicants included in this study sought the opinions of patients and the public on outcomes that should be included in their RCT. This greater role for patients and the public supports the increasing focus on the inclusion of patients and the public in the development of COS (20, 85). It also suggests that patients and the public could play an important role in the dissemination and implementation of COS.

Achieving full compliance by trialists to search for a COS when planning their RCT is likely to take time to achieve as trialists become accustomed to the process, and it may require a change in culture for consideration of COS to become standard practice in RCTs (116, 117).

4.5.2 Strengths and limitations

A limitation of this study was that the assessment was restricted to applications submitted to the NIHR HTA. Future assessments should also include applications to other funders. This will provide a wider view of the influence of funder recommendations on COS uptake.

We analysed data from two sources (application forms and a survey of applicants) but acknowledge that that was also limited to applications to a single funder, albeit the largest source of public funding for clinical trials in the UK. The survey included the need for the respondent to identify their project, which may have contributed to a non-response rate of 51%.

We did not carry out a comparison of the number of applicants mentioning COS before and after the recommendation was introduced by the funder. Given that the COMET Initiative launched in 2010, thus beginning to raise awareness of COS among trialists, we did not expect there to be many references to COS prior to the funder making their recommendation in 2012. Instead this study provides a baseline assessment for comparison with future assessments to monitor applicants' consideration of COS over time. Whilst it is possible that an applicant who had mentioned COS in their application would have used the COS regardless of the recommendation from the funder, we inferred that the funder guidance had been followed if the applicant specifically mentioned searching the COMET database which is the recommendation of the funder.

4.5.3 Summary and next steps

A funding body can have an impact on COS uptake by encouraging trialists to search for a COS. Funders could take further steps by putting processes in place to prompt applicants to be explicit about searching for COS in their application, thus alerting the funding board if a search has not taken place. The sources of information used by trialists to make decisions about outcomes in the absence of COS may suggest methods of dissemination for COS.

To build on the findings of this study, we endeavoured to explore the views of clinical trialists about COS and their development by conducting qualitative interviews. This will allow a deeper understanding of the barriers that may limit, and facilitators that may encourage, uptake of COS. The qualitative interview study is presented in Chapter 5.

Chapter 5: Exploring the barriers and facilitators to uptake of core outcome sets by chief investigators of RCTs: a qualitative study

5.1 Background

The studies reported in the previous chapters led to recommendations that further work be undertaken to identify interventions to improve the uptake of COS by clinical trialists. Implementation science seeks to facilitate the uptake of research findings and evidence-based practices in health care (118). For the study reported in this chapter, I therefore drew on implementation science to inform a systematic approach to the first steps in identifying the most appropriate interventions to improve the uptake of COS.

Behavioural research in implementation science places an emphasis on changing the behaviour of individuals in order to achieve a goal by identifying the most relevant interventions to generate the necessary behaviour change (119). Several behaviours are performed by clinical trialists when planning an RCT, for example, carrying out a systematic review, selecting outcomes to measure and submitting the RCT details to a clinical trials registry. It is the behaviour around the selection of outcomes, and choosing whether to implement a COS or not that is the focus of this chapter. To select the most appropriate types of intervention to facilitate a change in trialists' behaviour in implementing COS, it is necessary to first identify the barriers that hinder the use of COS from the perspective of clinical trialists. The barriers can then be mapped to the relevant behaviours. Intervention types can be chosen that will specifically target the behaviours that need to change. This can be achieved by applying a framework of behaviour change interventions.

5.1.1 The Behaviour Change Wheel: a framework of behaviour change interventions

The Behaviour Change Wheel (BCW) framework was developed following an evaluation of existing frameworks of behaviour change interventions. Based on a combination of 19 frameworks, it enables the selection of the most effective type of intervention, from all those available, that would bring about the required behaviour change to improve uptake (120). To achieve this the BCW has at its core the COM-B model of human behaviour which

describes Behaviour as the result of an interaction between i) physical and psychological Capability, ii) physical and social Opportunity and iii) reflective and automatic Motivation (120). Table 9 briefly describes each of these components.

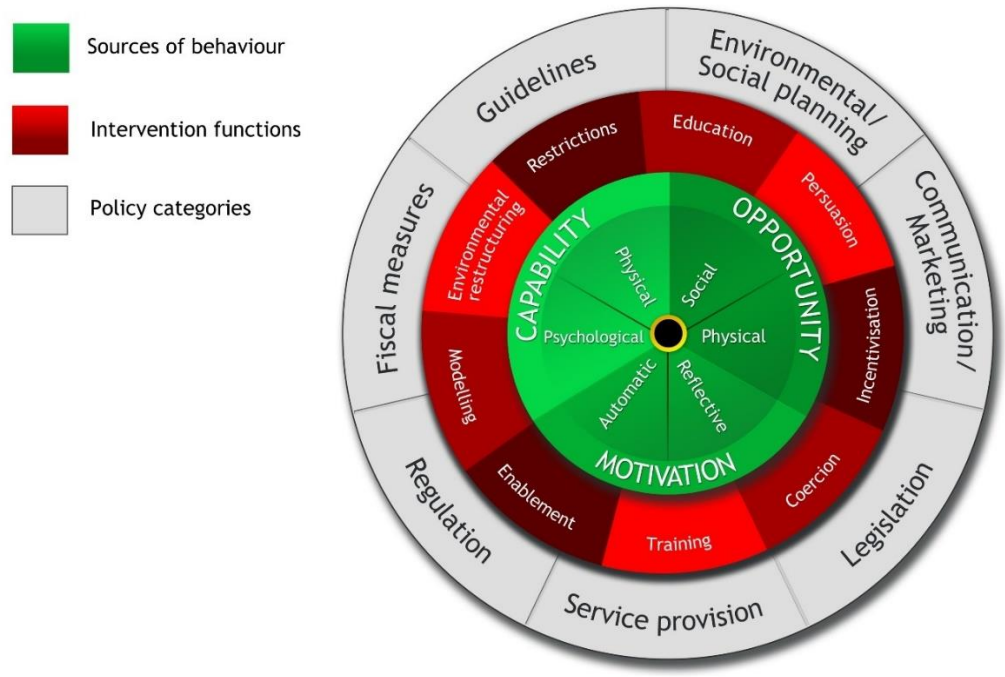
Table 9: The COM-B model of behaviour

Source of behaviour	Components	Definition
Capability: *being capable of performing the behaviour*	Physical	e.g. physical strength, stamina
	Psychological	e.g. knowledge, skills
Opportunity: *factors outside of the individual that make the behaviour possible*	Physical	e.g. time, location
	Social	e.g. cultural norms, social cues
Motivation: *the drive to want to perform the behaviour*	Reflective	e.g. planning, evaluating
	Automatic	e.g. desires, impulses

In the COM-B model, motivation refers to all of the brain processes that direct behaviour. Some of these processes are reflective, such as making plans, evaluations and conscious decisions (121). A result of reflective motivation might be deciding to buy a car based on its fuel efficiency. Other processes are automatic, such as emotional responses, desires, impulses and inhibitions (121). A result of automatic motivation might be following an unhealthy diet through habit.

Applying the COM-B model is believed to facilitate the identification of the components of behaviour that need to be targeted by an intervention to achieve the desired behaviour change. Around the COM-B model, which sits at the core of the BCW, are nine intervention functions that can be selected depending on the components of behaviour to be targeted (Figure 8). For example, education or training could be selected to target a lack of psychological capability. In the outer circle of the BCW are seven categories of policy, for example, guidelines that enable the interventions to occur. By mapping the characteristics of the intervention to the target behaviour, population and context, it is possible to ascertain which type of intervention is most likely to be effective in bringing about uptake. Once the appropriate type of intervention is identified work can begin to design a specific intervention and method of delivery.

Figure 8: The Behaviour Change Wheel Framework (120)



5.1.2 Behaviour change and COS uptake

Whilst behaviour change interventions in health care often target the health behaviours of individuals, for example, healthy eating or smoking cessation for patients, behaviour change interventions can also target the behaviour of health care providers. For example, studies have drawn on the BCW to develop interventions to improve adherence to screening guidelines by psychiatrists (122), implementation of smoking cessation care by health providers (123), uptake of a prescribing safety informatics tool by pharmacists (124), and implementation of infection and prevention control interventions by staff in a neonatal unit (125).

A systematic review published in 2017 (126) looked at the effectiveness of interventions that had been used to improve the uptake of standardised outcome measures by rehabilitation professionals. The interventions identified were either direct educational strategies, i.e. workshops and seminars, or indirect educational strategies via the dissemination of educational materials. Whilst nine of the ten studies included in the review that had measured the uptake of outcome measures reported improvements, the authors concluded that it was not possible to draw strong conclusions due to the weak designs of the studies. The review recommended that rather than relying on educational strategies alone, further work was needed to match the barriers hindering uptake of standardised outcome measures

to the most relevant behaviour change techniques, by using a framework for behaviour change interventions so that the most appropriate interventions could be identified.

While some previous work assessing COS uptake has suggested that it may be the characteristics of a COS itself that inhibits uptake by clinical trialists, for example increasing patient burden (68), other work has suggested that uptake may be influenced by trialists' behaviour, for example, lack of awareness or understanding of COS (58, 64, 72, 73, 76, 83). The BCW provides a starting point to investigate whether trialists' behaviour needs to be targeted by interventions to improve uptake of COS. Exploring the barriers to uptake can also identify what aspects of the wider health research system hinder uptake, e.g. at funder or journal level.

5.2 Aims

This study aimed to inform the first steps in developing appropriate interventions to improve the uptake of COS. This involved identifying the sources of behaviour, or characteristics of COS, that may inhibit uptake, and which the interventions need to address. To do this, I carried out qualitative interviews with chief investigators (CIs) of RCTs to explore the barriers and facilitators to uptake of COS, and where appropriate, mapped them to the relevant sources of behaviour.

5.3 Rationale for qualitative investigation

I applied qualitative methods to investigate the barriers and facilitators to the uptake of COS from the perspective of CIs of RCTs. Qualitative research considers the meaning that people attach to their experiences and informs the interpretation of behaviour (127). Previous work, reported in the systematic review in Chapter 2, suggested some barriers that may result in low uptake of COS. Carrying out qualitative interviews allowed me to explore in-depth the experiences of those involved in selecting outcomes and choosing whether or not to implement COS. Understanding the barriers and facilitators from the perspective of CIs is central to being able to develop interventions that would improve uptake.

5.4 Reflexivity

It is important to recognise that, whilst undertaking qualitative research, my own perceptions and beliefs play a role in shaping the results of the research (128). It is therefore

important that I reflect on my personal experiences, beliefs and biases and appreciate how they might have impacted on the interviewees and my interpretation of the data (129).

My introduction to COS began in 2010 during my role as an administrator which included providing support for the COMET Initiative. As a result of this role I attended all eight COMET conferences, sometimes proving support, sometimes as a delegate, and I also attended a variety of COMET management and committee meetings. Through these experiences I have developed a strong belief that COS have a positive effect on RCTs. For the purposes of the interviews it was important that I acknowledged my beliefs and tried to put them aside so as not to impress my own assumptions on the interviewees or interpretations of the data. I accepted that my beliefs would likely be challenged during the interviews and remained open to this.

To ensure that interviewees felt able to speak candidly, it was important that I made clear my position as a PhD student looking to learn from their experiences, rather than in any way representing the COMET Initiative, which may have provoked reluctance to share negative experiences of COS. This was done through the study information sheet and invitation email where my position as a PhD student was set out. I reiterated this to interviewees at the start of the interviews when introducing myself.

Whilst I had carried out a small number of interviews during my undergraduate degree, the interviewees there were people that I had an existing relationship with. As a PhD student interviewing CIs of RCTs, I found myself on occasion feeling apprehensive about the experience. To deal with this, I would spend some time at the start of each interview talking to interviewees about their research area and ongoing RCTs, not only to establish a rapport, but also to feel more comfortable myself.

Prior to commencing data collection, I attended training courses for conducting and analysing qualitative interviews with the Health Experiences Research Group at the University of Oxford. I drew on the training to inform my approach to conducting the interviews, for example, asking open and probing questions to explore participant's experiences. The training also informed my decision to draw on the thematic approach to analyse the interviews.

5.5 Methods

5.5.1 Interview format

The interviews carried out were semi-structured and topic guided. Unlike structured interviews, that focus more on fixed questions, the semi-structured approach is conversational using open-ended questions to encourage participants to freely describe their experiences (130). This was important to enable me to gain an in-depth understanding of the barriers and facilitators to COS uptake from the perspective of CIs.

The topic guide played an important role in ensuring that comparable topics were explored with each participant, but I asked additional questions based on participant's responses allowing me to explore unforeseen topics that arose during the interviews. The topic guide was informed by previous literature on the barriers and facilitators to uptake by clinicians, for example, of clinical guidelines (46-48) as described in Chapter 1, and literature on the BCW framework (120) (Appendix 9 for the topic guide). I opened the interviews by asking participants to walk me through their experiences of choosing outcomes for an RCT, which often led into discussion about COS. Where it did not, I steered the interview to the topic of COS by discussing a publication describing a COS that I had sent to participants prior to the interview and asking for their opinions about various aspects reported in the publication, for example, the methods used to develop the COS.

I conducted the interviews either via telephone or video-conference using Zoom (https://zoom.us/) depending on the participant's preference. Face-to-face interviews were not offered initially due to the varying locations of participants, though one interview was carried out face-to-face at the request of a participant who was based locally to me. Later in the study face-to-face interviews could not be facilitated due to the social distancing restrictions that had been put in place due to the COVID-19 pandemic. The interviews were audio recorded and transcribed verbatim. I carried out the transcription for the first three interviews as a way of becoming familiar with the data. Whilst it would have been ideal to do this with all transcripts the remaining interviews were transcribed by a professional transcription agency to ensure analysis of the interviews could be carried out in a timely manner. I made field notes during and immediately after the interviews to record my initial thoughts and ideas which I later used to assist with analysis.

As previously mentioned, I sent participants a publication of a COS that was relevant to their clinical area prior to the interview. Participants were invited to read the publication so that I could explore their views about how the COS was developed during the interview. If the participant had not read the publication the interview went ahead and I gave a brief summary of the publication during the interview.

5.5.2 Participants and recruitment

Purposive sampling involves selecting participants to take part in a qualitative research study because they have an in-depth knowledge or experience of the phenomenon being studied (131). The aim of this type of sampling is not to produce a representative sample, but to identify diverse, information-rich cases (132). I used purposive sampling to identify CIs whose experiences could offer insights into the issues that affect COS uptake and ensure that a variety of perspectives was captured, for example, variety in clinical area and the CI's experience of running RCTs.

Participants were eligible for recruitment if they were, or had been, a CI of an NIHR HTA-funded RCT. A UK-based sample was chosen because the COMET Initiative is hosted in the UK and is active in promoting COS to UK-based trialists. It is therefore more likely that trialists based in the UK would be aware of COS and have experience of the barriers and facilitators to implementing them in an RCT. NIHR HTA CIs were chosen as the NIHR includes a recommendation in its guidance to applicants about searching for and using COS. They were also the focus of the previous study reported in Chapter 4.

Initially I approached CIs of researcher-led RCTs, as outcomes for these RCTs are not initially recommended by the funder, but on discovering mention of COS in the protocols of commissioned RCTs, CIs for those studies were included in the sample too. CIs whose RCT did not have a relevant COS were not invited to interview. I determined whether a relevant COS existed by searching the COMET database using the disease name field and establishing whether the scope of the COS, i.e. research setting, population and intervention, matched the scope of the RCT. Where the COS did not report a fully defined scope, e.g. no intervention stated, I assumed that the COS was applicable to all interventions. I began interviewing participants in July 2019 and so restricted recruitment to CIs of RCTs where the start date was no earlier than January 2016, to aid with participant recall of their decisions in relation to the outcomes chosen for their RCT. The start date also needed to be at least one year after

the publication of the relevant COS to ensure CIs had time to become aware of the COS and implement it in their RCT. I invited CIs to be interviewed whether or not they had used a COS in order that a range of perspectives could be captured. Figure 9 shows the sampling frame.

I identified CIs by searching the online NIHR funding and awards database (https://fundingawards.nihr.ac.uk/search). I was able to filter the results in the database by start date, award type, and funding programme to ensure that the RCTs met with the pre-specified sampling criteria. I downloaded the results to an Excel spreadsheet and reviewed the title and abstract of each RCT and then searched the COMET Initiative database to determine whether a COS existed for the scope of the RCT.

Figure 9: Sampling Frame

RCT Funder NIHR HTA	**COS used in RCT** Yes/no
Funding stream Researcher-led Commissioned	**RCT Health Condition** Any with a relevant COS
RCT start date January 2016 or later	**COS** Any condition Published at least 1 year before RCT start date Developed for use in RCTs

I sent eligible CIs an email invitation (Appendix 10) with a study information sheet attached (see section 5.5.3). I continued to invite CIs to take part in an interview until data saturation had been achieved. Data saturation was deemed to be reached when no new data, and therefore, no new codes and themes, were identified during data analysis (133). It was not possible to fix the sample size prior to conducting the interviews, as it is not possible to predict when saturation will be reached. However, based on recommendations for sample size in studies aiming to achieve maximum variation, I expected to conduct between 12 and 20 interviews (134).

5.5.3 Ethics

Ethical approval for the study was granted by the University of Liverpool Health and Life Sciences Research Ethics Committee (Psychology, Health and Society) on 29/04/2019 (reference 4840).

An information sheet (Appendix 11) describing the study and how data would be used, processed, shared and destroyed was sent to participants by email along with a consent form. Participants were asked to return the signed consent form by email before the interview. I then signed the consent form and returned a copy to the participant. If the participant did not return the consent form they were given the option to give verbal consent. In the case of the two participants who chose to give verbal consent, I read each item of the consent form to the participant and asked whether they gave their consent. This process was audio recorded with the recording being stopped after consent had been given and restarted for the interview. Participants were advised that they could withdraw from the study at any time without giving a reason.

Anonymised transcripts of the interviews, electronic copies of consent forms, and the audio files containing verbal consent for two participants, are currently stored on the University of Liverpool Managed Network Service Filestore and will remain so for 10 years to allow for checking and queries with appropriate approvals. The audio recordings of the interviews were allocated a participant code and deleted once they had been transcribed. The transcripts were anonymised and assigned a participant code with all person, place and study names removed. Anonymised transcripts were accessed by me and my supervisors Paula Williamson (PW) and Bridget Young (BY). No identifying details are present in the write up of the results and quotes have been anonymised. At the end of the interview participants were asked if they would like to receive a copy of the study report.

5.5.4 Data analysis

My aim for the analysis was to develop an understanding of participant accounts rather than simply describe them. Interpretivism is a research paradigm in which researchers seek to understand how individuals experience the world (135). The interpretivist's epistemological assumptions contend that knowledge is shaped by human experience and social context (136). Unlike positivism, that argues reality is not influenced by the values of individuals (137), interpretivism sees reality as being what individuals perceive it to be (135). Whilst positivism is an objective approach that seeks to find causal relationships and high levels of generalisability, in my interpretative approach to the data I did not seek an objective truth. It was not possible to validate what participants said or make assumptions that the interviews gave direct access to what participants believe or think. Rather I saw the

interviews as offering insight into what the participants believe and think whilst recognising that their accounts should be interpreted in the wider context of the interview. For example, as I reflected in section 5.4, knowing my association with COMET, participants may have been reluctant to share their negative experiences or be critical of COS. As well as sharing their own direct experiences participants sometimes spoke in abstract terms about what they believed to be the experiences of others. I considered these accounts to add valuable insights, whilst recognising that they were not the first-hand experiences of the participant.

To analyse the interviews, I drew on the thematic approach in which patterns are identified from within the data, analysed and reported (138). The analysis occurred alongside data collection. As a starting point I approached the data inductively listening back to the audio recordings of the interviews and reading through the transcripts along with my field notes in which I had recorded my initial impressions. This enabled me to become familiar with the data. I then used line by line coding, to identify codes and categories within the data. For example, codes were developed when interviewees described learning about a COS through dissemination by a COS developer or hearing about COS from a funder, and these codes were grouped under a category for 'Awareness of the COS'. Developing codes and categories was an iterative process and new codes were developed and changes made throughout the process. The next stage of analysis involved deductive analysis informed by the COM-B model of behaviour as a coding framework. Codes and categories were assigned to the relevant component of the COM-B model, for example, 'Awareness of the COS' was assigned to psychological capability. All of the codes identified could be categorised within the coding framework that was informed by the COM-B model.

I carried out the process of coding and identifying themes and these were periodically discussed, along with the interview transcripts, with my supervisors PW and BY. I used NVivo 12 Pro qualitative data analysis software as a data management tool to facilitate coding (NVivo 12, QSR International https://www.qsrinternational.com/).

5.5.5 The quality of qualitative research

It is important to consider the quality of qualitative research. Opinions on how to define quality vary depending on the methods of data collection and analysis being used. Several criteria have been suggested to assess quality. For example, Lincoln and Guba focus on trustworthiness of the research findings with particular attention being paid to credibility,

transferability, dependability and confirmability (139). Alternatively, Yardley stresses the importance of sensitivity to context, e.g. the sociocultural setting of the research, commitment and rigour, e.g. in relation to the depth of analysis, transparency and coherence, e.g. of methods and data presentation, and impact and importance of the research (140). There is agreement across several criteria as to the importance of the definition and justification of study design, selection of participants and sampling approach and methods of data collection and analysis (141, 142). Each of these criteria were carefully considered during the planning and analysing of this study. Additionally, it is important to ensure quality reporting of qualitative research. To support this the Standards for Reporting Qualitative Research (SRQR) present 21 essential items to guide the reporting of qualitative research which were considered in the reporting of this study (143).

5.6 Results

Between July 2019 and February 2021, I interviewed 13 CIs of NIHR HTA-funded RCTs. The start dates of the RCTs ranged from May 2016 to April 2020 and they were assigned to the following NIHR-defined health categories: Respiratory (1), Musculoskeletal (2), Cancer (1), Reproductive Health and Childbirth (3), Injuries and Accidents (3), Skin (2) and Generic Health Relevance (1). Further details of the RCTs and COS are presented in Table 10.

Table 10: Details of COS and RCTs

Participant ID	Funding stream	No. years COS published before start date of RCT	Used COS (Yes, no, partially)
CI1	Researcher-led	5	Yes
CI2	Researcher-led	4	No
CI3	Researcher-led	11	Yes
CI4	Researcher-led	3	Yes
CI5	Researcher-led	11	Yes
CI6	Researcher-led	1	Partially
CI7	Researcher-led	<1 (involved in development)	Yes
CI8	Researcher-led	15	No
CI9	Researcher-led	1	Partially
CI10	Researcher-led	10	Partially
CI11	Commissioned	1	No
CI12	Commissioned	2	Yes
CI13	Commissioned	1	Yes

The interviews lasted between 26 and 54 minutes. Data saturation was reached after ten interviews. I carried out two more interviews to check that no new data and codes were

identified. One further interview was conducted as this had previously been agreed with the participant.

Barriers and facilitators to uptake of COS were identified as informed by COM-B components: capability (psychological), opportunity (social) and motivation (automatic and reflective).

5.6.1 Capability

CIs did not mention any barriers or facilitators to physical capability in connection to using COS. Barriers and facilitators to physical capability often relate to having the physical strength and stamina to carry out a behaviour and it was not surprising that these factors did not feature in CI's experiences of implementing COS. However, CIs did discuss a number of factors linked to psychological capability, i.e. the knowledge and skills needed to implement COS. These related to a CI's awareness of COS, their understanding of the need for COS and their skills to use COS.

Awareness of COS

"I think there is broad awareness of them, certainly in the clinical trials community"

CIs demonstrated an awareness of COS, with all but one reporting having heard of COS prior to their interview. The CI who was not aware of COS spoke about this being their first RCT as a CI. They explained that they had received feedback from the funder on their choice of outcomes, though the funder did not query the absence of the COS. This CI also spoke about taking advice from patient research partners about which outcomes to include. The CIs who were aware described a number of ways in which they learned of the COS.

Some CIs explained that they, or a co-investigator on their RCT, had been involved in the development of the COS. This ranged from leading on the development of the COS: *"We also had (…), who is a co-investigator, so she co-led the (…) guidelines" (CI5)*, to being involved in other aspects of development, such as work around the choice of an outcome measurement instrument to be recommended by the COS.

CIs also spoke about some of the ways in which COS developers had disseminated details of their COS to raise awareness amongst CIs. Some CIs had accessed the dedicated COS website set up by the COS developers, whilst others became aware of the COS via reading the publication and social media. CIs had also attended meetings set up by the COS developers

to specifically disseminate the COS, or the COS was presented at a wider conference for the clinical area that the CI had attended: *"I went to the (…) national conference in (…) and the core outcome set was published as an abstract there" (CI12).*

Some CIs referred to external organisations that had raised their awareness of the COS. These included funders, the NIHR Research Design Service (RDS), the COMET Initiative and Clinical Trials Units (CTUs):

> *"You know, a bid run through a CTU, someone will say somewhere, "Have you looked for a core outcome set here?"" (CI9)*.

As well as individual COS developers and wider organisations, CIs also discussed ways in which the research community played a role in raising awareness of COS. This included through communication among colleagues and peer support:

> *"The community has a responsibility as well. People, who are aware of it, making others in their network aware of it." (CI6)*

> *"So, what happens now, is, so when I'm helping people write grant applications for things – we're all doing it; the word is out there." (CI10)*

Understanding of the need for COS

"It just standardises and makes it so that people can actually compare different studies"

CIs indicated their awareness of the problems around outcomes in RCTs and their understanding of the ways in which COS address those problems. One of the issues highlighted by CIs was the inconsistency of outcomes measured across RCTs and the difficulty this caused in making comparisons across trials:

> *"You have got two trials that have reported this and one that has reported that and three…you know, it's all bitsy when you try to put it together." (CI7)*

One CI explained how inconsistency of outcomes led to difficulties for them when trying to synthesise evidence:

"No, we're doing our best at the moment to do a network meta-analysis on that but obviously, you can imagine, it's very limited by the state of the outcome measures." (CI11)

CIs spoke about the role of COS in addressing inconsistency of outcomes across RCTs. When talking about the advantages of COS, CI6 explained: *"There's the knock-on of being more consistent, so that would help with evidence synthesis and help reduce waste."*

While inconsistency of outcomes was a recurring theme in the interviews, one CI pointed out that this was not the case in their clinical area as: "*There are very few outcomes"* and as a result RCTs were including the same outcomes: *"because that's the only thing you can measure" (CI10).*

A further problem that CIs referred to as being addressed by COS was the relevance of outcomes included in RCTs. One interviewee, CI6, described COS as helping to "get it right first time" by not missing outcomes that are important. CI6 further pointed out that COS could help CIs who were less experienced in a certain clinical area, population or intervention to understand which outcomes are most important for their type of RCT:

"People, maybe, coming to a new area, a new population, or a new intervention type, they're not really sure what things- They might have a general idea of what they want to measure, but it just helps get them into that space and know what other people consider the important things." (CI6)

Understanding of how to apply COS

"They're just saying this is the minimum data set"

CIs indicated their understanding that using COS does not preclude the measurement of other outcomes in an RCT. CI6 referred to the importance of making this clear so that it did not result in other outcomes that may be important to a particular RCT being missed:

"If people view it in the way that they're the only ones that should be measured then they could, potentially, do a study where it would've been useful to add in some additional measures which were particularly relevant to their group or their

intervention. You don't get that data then. That shouldn't happen if they're applied as intended." (CI6)

One CI explained how this potential misunderstanding had been addressed from the outset by the developers of the COS that they had used:

"I think they can be misread and I think (…) have been very clear about that, they're saying you don't have to choose (…) for example as your primary outcome but you certainly want to you, you need to include it so the trials can be compared" (CI1)

Whilst CIs indicated their understanding that all outcomes recommended by a COS should be measured, as a minimum, one CI suggested that: *"you have to be given the right to pick and choose" (CI10),* depending on what outcomes are suitable for the particular RCT and whether the RCT team agree with the recommendations. They spoke about how they and their team decided not to use all of the outcomes, instead viewing the COS as a list from which to choose:

"So, some things we put in and some things we didn't, so we didn't use all of them, we just pick and choose." (CI10)

Linked to this, CIs explained that it was important to assess the applicability of the COS rather than *"pick it off the shelf and use it without it being checked" (CI3)*. This included critiquing the methods used to develop the COS and ensuring that the COS was up to date. CI4 pointed out the importance of assessing the applicability of a COS for the particular RCT, rather than using a COS in order to "tick a box":

"Understand it first and if something then in existence fulfils your needs, then that's great. The tick box world is not something personally I'm a big fan of. I like to look at things in a bit more detail and decide whether it's appropriate for what I'm doing." (CI4)

CI4 continued to discuss the implications of measuring outcomes that were not relevant to the RCT, highlighting the time and resource that goes into measuring outcomes meaning

that: *"The last thing you want is an outcome measure down there which has absolutely no purpose for you … it's not going to help me with this particular question." (CI4).*

This was echoed by CI6 who explained: *"When setting up a trial, I would always search [for a COS] and I'd always reflect on what I find."*

5.6.2 Opportunity

As with physical capability, CIs did not mention any barriers or facilitators to physical opportunity, such as those relating to time or location, in connection to using a COS. However, a number of factors were raised that linked to social opportunity, i.e. the outside factors such as cultural norms and social cues which influence behaviour. These related to support from external organisations in the wider health research system and the research community.

Support from external organisations in the wider health research system to use COS

"I think the funder recommendations do have value"

CIs spoke about receiving support from external organisations within the wider health research system in relation to their use of COS. One type of organisation referred to for providing support through their recommendations to consider COS was funders of RCTs:

> *"We had some feedback from the funders that we should consider the core outcome set." (CI2)*

> *"And there is this drive by the NIHR to say that you need to use a core outcome set in your outcomes." (CI12)*

Whilst on the whole CIs expressed their agreement with CI4 and CI6 that "a gentle recommendation" from the funder to "check, and use where relevant" is the preferred approach, CI12 did not agree that not using the COS should be a choice for the CI to make: "I think there shouldn't be that option" unless there are "exceptional circumstances":

> *"And I think, if the funders hold central to those kinds of things, and say that you can't do a (…) trial without doing a longer-term outcome, then it will help, won't it?*

Because if they don't fund anything that doesn't have that outcome in, then longer-term research quality and usefulness will get better." (CI12)

However, some CIs expressed concerns about the idea of funders making COS compulsory:

"Once you go down that route, unless it is perfect and everybody accepts it, then you're in a bit of trouble." (CI4)

"As soon as you say, "This is the right thing you should do in all of these situations," I think you then restrict the scope of what you can actually ask and answer." (CI9)

As well as funders, CIs mentioned support from journals to use a COS. CI13 spoke about how journals in their clinical area had agreed to promote the use of COS:

"So, journal editors then signed up to it and said, "Well we're going to promote this"." (CI13)

CI12 referred to this "buy-in" from journals as being one of the reasons for wanting to use the COS:

"And there has been buy-in from the journals, so I think we wanted to be- To make sure that our research kept pace with it." (CI12)

Support from the research community to use COS

"I think, if it became like the industry standard like the widely appreciated thing to do"

One CI spoke about COS becoming the 'norm' as facilitating their uptake:

"Yes, if it became a more widely accepted thing, that would probably influence other people more." (CI6)

This relates back to the earlier point of raising awareness through peers in the research community which could also provide social opportunity to use COS:

"The community has a responsibility as well. People, who are aware of it, making others in their network aware of it. It's not just the people who run the website, it's spread through communities of practice as well." (CI6)

5.6.3 Motivation

During the interviews CIs referred to factors relating to both automatic and reflective motivation.

5.6.3.1 Automatic motivation

CIs spoke about barriers and facilitators that may affect the uptake of COS that related to automatic motivation, which comes from automatic brain processes, such as desires, impulses and urges. These related to territory and moral obligation.

Territory

"I want to do it my own way, it's a bit better."

Some CIs spoke about territory as a barrier to COS uptake. This related to situations where CIs may have developed their own outcome measurement instruments that had not been included in the COS. One participant suggested that in this situation CIs may choose their own, or preferred outcome measurement instrument, over those recommended by the COS:

"The problem is when groups get together and try and decide them, is that inevitably people that have developed measures that are then not selected can obviously feel a bit put out" … "even with the best will in the world you, you can be biased towards your own measure and may not be as objective as you could be around how well it actually works in clinical trials or other settings." (CI1)

This suggestion of territory also linked to CIs wanting to have control over their own decisions rather than following guidance that they had not been involved in creating:

"But then you know when you get one particular person who's like, "I'm not going to have anything to do with that group," and they go off on a tangent on their own." (CI3)

"It wasn't their idea, and so they are not going to support it or whatever." (CI7)

One CI suggested that this could even be the case when a CI had been involved in the development of the COS but did not agree with the outcomes included:

> *"Maybe you're even involved in the development process and you were that person who didn't get what you wanted, so you do it your own way." (CI6)*

Moral obligation to use COS

"I think there's a bit of a moral obligation there"

As well as barriers relating to automatic motivation, one CI spoke about moral obligation as a facilitator to COS uptake. They explained that even in situations where a CI might prefer a different outcome measurement instrument, they should put this aside so that the benefits of COS can be realised:

> *"I think the other responsibility trialists have as well is, as far as possible, trying to respect the recommendations and including them in your trial even if it's not your favourite outcome measure, because I think there's a bit of a moral obligation there to the greater good to help then in years' time the evidence to be drawn together more easily or interpretation of different studies be more easily able" (CI1)*

5.6.3.2 Reflective motivation

Reflective motivation relates to reflective mental processes, such as plans and evaluations. When CIs spoke about their evaluations of COS, they described barriers that related to the characteristics of COS rather than barriers that related to behaviour. In this section, two overarching themes are presented in relation to CI's appraisals of COS; the drawbacks of using COS and the COS development process.

The drawbacks of COS

Though CIs spoke about certain benefits that they believed COS may provide, for example, "pulling up the quality" of research "to a level which might be acceptable" and helping with justification of outcome choice, they also spoke of drawbacks that may inhibit their uptake.

- **Patient burden**

"I'd draw the line if it was actually going to be burdensome for the patient"

Patient burden was a recurring theme throughout the interviews. Whilst CIs indicated an understanding that COS are a minimum set of recommendations, and other outcomes relevant to their RCT could be measured in addition, some expressed concerns about COS creating burden for patients. CIs spoke about different ways in which burden could occur, including the possibility that COS might lead to an increase in the number of outcomes that patients were being asked to complete:

> *"I think that is a real challenge, it's a real issue in core outcome sets, that you end up with a list that is so long that you struggle with burden … so the question is, is a core outcome set actually making us add too much, add too much burden?" (CI9)*

> *"So, I'm already thinking this is way too long and I can't add anything else in because it's already way too long. So, that's my only irritation with the core outcome set." (CI11)*

Further concerns around patient burden related to repetition across outcome measurement instruments that may occur when the number of outcomes increases. CIs expressed concerns that this may result in patients being less likely to complete the outcome measurement instruments:

> *"It looks, with a lot of questions, like a lot of the things will be repeated. And I think that does annoy patients a bit. I've certainly seen in other studies, where they've said, "You've asked me this question, why do I have to go through it again?"" (CI9)*

> *"Participants certainly don't like it if they're filling in a 50-item questionnaire and feel the first 20 items are repetitive …" (CI1)*

In addition to the number of outcomes, and the repetition that may cause, CIs spoke about the importance of outcomes being relevant to patients. They spoke about how patients may lose motivation in completing outcomes measurement instruments if they are not invested in the information they are being asked to provide:

"There's the meaning for the patient as well. If they're answering questions they don't feel have any meaning, they're less incentivised to complete it. You can always tell they're just not very comfy doing it." (CI4)

This concern about patient burden was highlighted as an important barrier which could influence a CI's decision to use the COS:

"So, if burden became a problem, then I would say I will sacrifice my commitment to the core outcome set." (CI9)

In contrast, CIs were more comfortable with an increased number of outcomes if collection of those outcomes did not impact upon the patients:

"I don't think it's a big burden on patients, because most of it comes from records." (CI7)

"because that isn't something that's collected by patients, you know, it's the research team members that are collecting that, that's okay I think." (CI1)

Furthermore, CI13 pointed out the benefit of asking patients to report outcomes in ensuring that patients' voices are heard:

"The patient-reported outcomes are what the patients have to contribute, but we never thought of that as a burden, we always thought of that as, "This is something great that we're doing because we're giving patients a voice." (CI13)

- **COS becoming outdated**

"Well, the problem is they're out of date"

CIs spoke about their concerns around COS being, or eventually becoming, out of date as technology progressed and new outcome measurement instruments were developed. As CI1 pointed out, *"there's always a possibility that what's recommended now won't be recommended in five- or ten-years' time."*

Although seeing the benefits of COS: *"So I love them, I like the idea of core outcome sets"*, CI3 went on to explain the problem with a COS that was relevant to one of their RCTs becoming out of date:

> *"but it never really kept up to date. It needed to be looked at every couple of years just to check which ones were in it, which ones weren't."*

Linked to these concerns about the currency of COS, CIs spoke about the importance of revisiting COS periodically and making revisions where necessary. CI7 pointed out: *"they are not permanent bodies of knowledge" "They shouldn't be set in stone, so that we may actually, perhaps we should be coming back to the beginning and re-evaluating rather than continuing to build new ones."*

As well as considering advances in technology and outcomes measurement instruments, one CI felt that it is important to consider that what is significant to patients may change over time too:

> *"what was important to patients in 1997 probably has changed, because our technology has changed so much" … "And that changes the discussion with patients, because then they start to value other things, they start to value high-level activities" (CI9)*

Whilst CIs spoke about the importance of updating COS, CI13 pointed out some of the difficulties with this process, including decisions about when an update would be appropriate:

> *"Updating of core outcome sets is a very tricky area because how do you say that this is now the time to update, is it the opinion of two experts or do you…? … I think it's very difficult to define at what point there is enough evidence and opinion to warrant a change, because it's subjective." (CI13)*

In addition, CI13 spoke about the problem of deciding who should be responsible for updating the COS:

"Then the other thing is, what about ownership? I mean, okay, somebody has developed a core outcome set and it's out there. Then another group comes along and says, "Well this is all outdated, I want to do another core outcome set." … Who decides that a core outcome set I've developed is now obsolete? It is extremely tricky and it could turn very political as well." (CI13)

As a potential solution, CI13 suggested that a structure should be put in place to regulate the updating of COS:

"I almost feel that structure is what's needed with core outcome sets but is lacking as far as I know … So perhaps it then becomes the responsibility of a COMET board of some sort to look at applications for updating these core outcome sets, and then justifications for it, before saying, "Okay, we will let you proceed" … That authority has to be recognised, otherwise it can all just disintegrate into complete chaos." (CI13)

COS development process

CIs spoke positively about the practical methods typically used during the COS development process. They felt that consensus methods involving a range of perspectives were appropriate. However, CIs referred to other aspects of the development process that could present barriers to COS uptake.

- **The suitability of COS**

"I'm just worried that you can't do it on everything"

Some CIs expressed concern about COS being developed *"because there is a gap in the market" (CI4),* that COS developers then try to fill, without first investigating whether a COS is in fact needed. CI13 described how some COS developers decide to develop a COS for a condition before carrying out investigations to determine the state of outcomes reported by RCTs in the clinical area:

"They decide to develop a core outcome set and then they work backwards and they say, okay, well we'll do a systematic review in this area and see what the findings are." (CI13)

Linked to this, some CIs questioned whether a COS would be suitable in all situations:

> *"I'm just worried that you can't do it on everything. If you were doing epidemiologically based research where you're looking at big signals and big wide population-based questions, I think it does work. I think to pick something and say you have to have these things in, if you were doing a piece of research on surgery for instance and to say you've got core outcome measures for surgery, I just don't think it works." (CI4)*

Later in their interview, CI4 elaborated:

> *"What I also think core outcome measures do is they try and encompass too many different fields. For instance, surgery, it's hopeless to say we're going to have a core outcome measure set for surgery in general. That can go from dentistry to major heart surgery where you're measuring very different things. I think there's a level of concepts and people get a bit carried away with that." (CI4)*

Whilst reflecting on this, CI4 spoke about their experience of being invited to take part in the latter stages of the development of a COS where it became apparent that a COS would be difficult to implement in the specific scenario. They suggested that more thought needs to be given to this right from the start as COS may not always be appropriate and this should be considered prior to initiating the COS development process:

> *"What needs to happen is probably there needs to be as much attention paid to the topic itself before anything is done, whether it's appropriate to have a core outcome set for that particular thing they're trying to do it for." (CI4)*

Related to this, CI12 suggested implementing a structure for deciding on the areas for which COS should be developed:

> *"But I think there needs to be some central prioritisation of certain outcomes sets to be developed through."*

- **Engagement with clinical trialists**

"I think there's a thing about engagement here, that is a real problem"

A common theme throughout the interviews was the lack of engagement that CIs felt with the COS development process. CIs did not feel that they had to be involved in the development themselves, but want to know that their field had been represented if they were expected to use the COS:

> *"I think there's a thing that a lot of (…) feel that this is developed by people who don't actually- who aren't involved in our world. And I think there's a thing about engagement here, that is a real problem." (CI9)*

> *"The problem we have is that these guidelines are basically written by what I call the 'usual suspects', so it's the same people who go round telling everybody what to do, so they have no clinical exposure whatsoever, they just go around telling everybody else what to do. So, it's really interesting that the justifications for this paper is that experts have called for this. It's the same experts calling for it who are actually answering it." (CI10)*

This lack of engagement was seen to create a barrier to CIs who felt that their views had not been represented:

> *"I think a lot of (…) will look at the list of names, not find a (…), or not obviously see a (…), and disengage." (CI9)*

Some CIs felt that, no matter how well the development of the COS was carried out, without full engagement from those who will be the users of the COS, there would likely be problems with implementation:

> *"you can do the process, you know, very actively and very well but if, you don't get engagement from the community that you're going to want people to take it up then, you know, it might be time wasted." (CI1)*

- **Completing the COS development process**

"It was a lovely idea that didn't get very far"

CIs spoke about their expectations of COS and what they hoped to gain when a COS had been developed for their clinical area. As well as the 'what' to measure, some CIs said they had hoped the recommendations would include the 'how' to measure. In part this related to achieving full consistency in outcomes and their measurement instruments:

> *"It's all well and good having, say, health-related quality of life in all studies, but if everyone measures it a different way then you might be left with the same problem of not necessarily being able to combine data from different quality of life tools." (CI6)*

> *"A bad drawback is that the principle and the idea is sound but, until the outcomes have definitions, then it hasn't quite reached the level yet. So, that's the disadvantage, is that- And I would kind of like it to stop, saying, "We don't need any more core outcome sets developed, we need to work on the ones we've got." I think that would be a really brave statement, but I think it should be said." (CI12)*

However, other CIs spoke of their reluctance in relation to COS recommending 'how' to measure in the event that the outcome measurement instruments were not suitable. This was the case for one CI who had experience of an outcome measurement instrument being made compulsory in their clinical area at one time, though not via a COS:

> *"It was very poorly put together, but every journal recommended or even enforced you to have this outcome measure. Again, you do it because you've got to get the work published, but it was a very poor score." (CI4)*

They went on to express a preference to have the 'what' alone recommended:

> *"It could be if you're a doing a cost effectiveness analysis you have to have an instrument in there which will allow you to do that, an EQ-5D, that might well be it. It doesn't have to be named as that, it just has to be a cost effectiveness and general health questionnaire." (CI4)*

Additionally, CI13 pointed out that, as with outcomes, outcome measurement instruments can become out of date and require monitoring in the same way:

"So, definitions are great, and I think it's important to have them, but I've just learned that, in a field that's potentially evolving, creating definitions at one time isn't all a perfect system. Even the definitions may change over time, so you need to update what outcomes and how you define them in the future." (CI13)

Linked to recommending the 'how' to measure, CIs spoke about COS development presenting an opportunity to improve the quality of outcome measurement instruments. A common theme throughout the interviews was the lack of high-quality outcome measurement instruments in a number of clinical areas, and one CI expressed disappointment that the COS had not led to improvements:

"They didn't actually say which measures we were using for each of them. In some areas, they say, "Oh, we need to make a new measure for that" and then, you know, five years later, I don't think anyone has started that." … "I looked more at the overall domains and the fact that they couldn't tell me all the measures. I just thought, right, this is not really helping me very much, when are you going to do some more? When are you going to find us some good measures? So, the fact that it wasn't delivering, for me, was more important than the process." (CI11)

While hoping that COS would encompass outcome measurement instruments as well as recommending outcomes, CIs spoke about the difficulties that developers face in fully committing to that whole process of COS development. One factor that CIs referred to was the lack of funding available to support the development of COS. One CI, who had been involved in the development of a COS, explained why their COS had not yet gone beyond recommending the outcomes:

"It would be great if someone came to us and said, "You've done the core outcome set for (…), we'd really like to support the funding to develop a measure and 'how to measure'". We would think that was- And we have put lots of applications in to do it, and the funding sources just don't come easily. Who then updates and keeps things going" (CI12)

Linked to the lack of funding to develop COS, some CIs pointed out that lack of funding also prevents COS being updated:

> *"The problem is there seems to be funding for them to get started, and then there doesn't seem to be funding for them to be maintained. So, they'll obviously then go out of date a bit." (CI3)*

Along with funding, CIs suggested that the "extensive process" involved in the completion and maintenance of COS was also difficult because often junior researchers begin the process as a PhD project and need to move on before the COS is completed, i.e. recommendations are made for 'how' to measure or updates to the COS:

> *"I think that's just something to consider because research fellows who put core outcomes together may not be the people who then, when- After they finish their PhDs, move on and do other things. If they get into that area of research, well and good. Then the question becomes, "Who takes the responsibility for updating these core outcome sets if it's a research fellow who was just doing their PhD thesis and has moved onto other things?" (CI13)*

CI13 suggested that COS were more likely to be completed and maintained if the developers were part of the research community for which the COS had been developed:

> *"I think it's important that the people who are developing these core outcome sets are the people who are actually integrated into research in this area and clinics in this area, because that keeps them up to date, that keeps them motivated to change things." (CI13).*

This was echoed by CI4:

> *"What you don't want is people who just go around jumping from one area to the next putting together a core outcome set." (CI4)*

5.7 Discussion

5.7.1 Main findings

In-depth qualitative interviews identified barriers and facilitators that influenced CIs' use of COS in RCTs. Interventions to improve uptake of COS should be informed by these barriers and facilitators.

The application of a behaviour change framework enabled a theory-based approach to discover appropriate types of interventions to improve COS uptake. Informed by the COM-B model of behaviour the interviews identified barriers and facilitators to the uptake of COS linked to the capability, opportunity and motivation of CIs. As well as relating to the behaviour of CIs, barriers also referred to the characteristics of COS that were beyond a CI's direct control.

According to the COM-B model of behaviour it is necessary to have the psychological capability, i.e. the knowledge and skills, to perform a behaviour. The interviews identified facilitators relating to a CI's psychological capability that enabled their use of COS. Enablers included being aware of COS, understanding the need for them, and knowing how to apply them.

CIs described several ways in which they had learned of COS, with some CIs or their co-investigators having been involved in COS development. The COS-STAD guidance on the minimum standards for the development of COS recommends that those who will use a COS in research should be involved in its development (19). This is to help ensure that the most relevant outcomes are included in the COS. However, my findings indicate that involving clinical trialists in COS development has the potential to also improve uptake. As well as raising awareness of the COS, involving trialists in their development addresses a barrier that was identified through CIs' reflective evaluation of the COS development process relating to engagement. CIs described disengaging with a COS if their role and clinical specialty had not been represented in its development. Therefore, inviting trialists to be involved in the development of COS can encourage its uptake through raising awareness and engagement, ensuring that all clinical roles and specialties where the COS might be applicable are represented throughout the development process.

Alongside involvement in COS development, CIs mentioned several ways in which the COS had been disseminated by the developers that had raised their awareness. These included via a dedicated COS website produced by the developers, through publication, social media and at conferences, including meetings set up by the COS developers and wider conferences for the clinical area. These methods of dissemination align with recommendations following a survey of COS stakeholders who were asked to suggest dissemination ideas (144). It is important that COS developers plan their dissemination strategy and consider these methods to maximise awareness of the COS.

One of the CIs interviewed had not previously heard of COS. Unlike the other participants, this was the first time this interviewee had been a CI of an RCT. New CIs who may not yet be fully engaged in the RCT community will likely have had fewer opportunities to become aware of the COS through peer support. They are reliant on the dissemination of the COS by the developers reaching them. As an additional option, the BCW recommends education as an intervention to tackle gaps in psychological capability. Including COS in educational programmes for researchers, particularly those aimed at new CIs, provides the opportunity to increase awareness and knowledge of COS and their purpose. Furthermore, educational courses could facilitate understanding of how to apply COS. Though the CIs interviewed indicated an understanding that the outcomes recommended by a COS are the minimum that should be measured, some expressed concerns that outcomes that are important to a particular RCT, that are not represented by the COS, could be missed if this is not made clear. As well as COS developers being explicit that their recommendations are a minimum, educational courses could reinforce this message.

Reflecting on the COS recommendations before implementing them to ensure they were applicable to their RCT was discussed by some CIs. Linked to this, were concerns about situations arising where COS may be implemented in RCTs where they are not appropriate because an assessment of suitability had not been carried out. This may relate to the quality of a COS, e.g. in terms of how the recommendations had been reached, as well as the relevance to the particular RCT. The COS-STAD recommendations can assist CIs in assessing the quality of a COS, but currently no guidance exists on how to assess the applicability of a COS. This may not be straightforward in instances where the scope of a COS is a partial match with the scope of the RCT or there are several COS for the same condition. Training is another intervention recommended by the BCW to improve psychological capability by imparting

skills and an intervention function suggested to achieve this is guidelines. The production of guidelines advising on how to assess the applicability of a COS could be used alongside the COS-STAD guidance for assessing quality.

In addition to facilitators relating to capability, CIs discussed enablers to COS uptake linked to social opportunities provided by the wider health research system. Specifically, funders and journals were referenced as facilitating the implementation of COS. Some CIs had received feedback from their funder that had recommended they consider the COS for their RCT. However, it appears that such feedback is inconsistent. In the case of the CI who was not aware of COS, feedback had been received from the funder about outcomes, but the funder did not recommend the COS. Furthermore, the recommendation to consider COS in the funder's guidance document had not been picked up by the CI. As suggested in Chapter 4, following the review of NIHR HTA funding applications, funding boards could facilitate COS uptake by informing CIs where a COS is available but has not been referenced in the application. The recommendation to consider COS could be included in the outcomes section of the application form where it would be more noticeable.

Reflective evaluations of COS carried out by CIs identified barriers to uptake that related to the characteristics of COS. These barriers are beyond the control of CIs and instead need to be addressed through the COS development process.

Patient burden was identified as a concern for CIs, relating to the number of outcomes recommended by a COS, repetition across outcome measurement instruments and the importance of the outcomes to patients. Patient burden was touched on in Chapter 2 as being a potential barrier to uptake as identified in the systematic review. As cautioned in Chapter 2, restricting the number of outcomes in a COS may risk the exclusion of a crucial outcomes. It is also important to consider whether limiting outcomes would stifle the voice of patients through the curbing of patient reported outcomes and other outcomes that are important to patients. In order to address patient burden, when selecting outcomes and measurement instruments it is important that COS developers consider the demands placed on patients. To ensure the outcomes included in the COS are meaningful to patients, it is important that patients are involved in the development of COS and input into what outcomes and measurement instruments are recommended.

Often COS developers address the first stage of a COS, i.e. recommending *what* outcomes to measure but most do not go on to the second stage of recommending *how* to measure them. This presented a barrier for some CIs. A systematic review of methods used to select outcome measurement instruments for COS found that of the 337 published COS studies, 118 (35%) had completed both the *what* and *how* stages (145). CIs suggested that it was important that COS recommend outcome measurement instruments to ensure consistency in how the outcomes were being measured. As noted in Chapter 2, the COMET and COSMIN Initiatives have co-produced a consensus-based guideline to assist COS developers in selecting outcome measurement instruments. Some CIs spoke about a lack of quality outcome measurement instruments available for their clinical area and their hopes that this would be addressed by the development of the COS. Where COS developers find this to be the case they should take the opportunity to add the development of new instruments to a research agenda.

Whilst completing both stages of the COS development process might be preferred, some issues that CIs were aware of that would hinder developers' efforts to do so were identified. These included lack of funding for COS development projects and difficulties for COS developers in committing to completing both the *what* and *how* stages of COS development. Even when funding is available for the initiation of a COS development programme, it may be that the funding does not stretch beyond agreeing what outcomes should be included in the COS. It may be helpful for COS organisations, such as the COMET Initiative, to identify appropriate funding sources and liaise with funders to raise awareness of COS and the importance of having funding to develop them in full. Often a COS will be developed as a PhD project and the developer does not have the resources to commit to the remaining stages of the COS at the end of their PhD. Developers should endeavour to include in their research team individuals who are invested in the clinical area and have an interest in ensuring the COS process is complete.

Linked to the consideration of who should be involved in leading the development of COS were concerns about developers moving from one COS to another without full consideration as to whether a COS is required. Further concern was raised about COS being developed because one does not already exist rather than first investigating whether there is the need for that COS. For example, one CI explained how there were few outcomes that could be measured in their clinical area and so RCTs were already measuring the same outcomes.

Before starting the COS development process, it would be prudent for developers to carry out investigations into whether a COS is needed, for example, by engaging with clinical trialists and systematic reviewers and assessing the state of outcomes in the area.

Alongside completing the COS in full, CIs spoke about the need to review and carry out updates of the COS to ensure that the recommendations remained current. This was in relation to advances in technology, the development of new outcome measurement instruments, and changes to patients' priorities. As with completing the full development of a COS, problems with updating them were also identified by CIs who had been involved in COS development. For example, issues around who should take responsibility for deciding whether and when an update was necessary would need to be resolved. A potential solution would be for a COS organisation, such as the COMET Initiative, to structure the process by receiving and assessing applications to update existing COS. Only with approval, following liaison with the original COS developers, would the revision go ahead.

A facilitator to uptake identified during the interviews, linked to social opportunity, was COS 'becoming the norm'. This notion aligns with that of culture change as identified in an interview study exploring the implementation of COS in haemodialysis (117). The authors recommended that COS uptake should be an organic process arising from a shift in the mindset of clinicians. Through support from peers and the wider research system, over time a change in culture could further improve the uptake of COS.

5.7.2 Strengths and limitations

The qualitative interviews and analysis provided insights into the barriers and facilitators that influence COS uptake from the perspectives CIs who have experience of choosing outcomes for an RCT. Unlike in the survey reported in Chapter 4, I was able to use open-ended questions to encourage participants to openly share their experiences and further explore unanticipated topics that arose. By using the BCW framework to inform the study, the study has enabled theory-based recommendations for interventions to improve uptake to be suggested.

A limitation of the study is that participation in the interviews was limited to CIs who were based in the UK and whose RCTs had been funded by the NIHR HTA. UK-based CIs are more likely to be aware of COS and have experience of implementing them owing to the work of

the COMET Initiative in the UK. In countries where there is less awareness of COS, the barriers and facilitators to uptake may differ. Further work is needed to investigate barriers and facilitators to uptake of COS in settings beyond those in this study.

5.7.3 Summary

Barriers and facilitators to the uptake of COS by CIs of RCTs were identified in relation to capability, opportunity and motivation, all of which influence behaviour. Some barriers and facilitators were associated with the behaviour of CIs and can be targeted by behaviour change interventions. Others were associated with the characteristics of COS that should be addressed by the COS development process, and the wider research system. Table 11 presents a summary of the suggested actions to improve COS uptake.

Table 11: Summary of suggested actions to improve uptake

Who	Action	Intention that will improve uptake of COS
COS developers	Invite clinical trialists from all clinical roles and specialties relevant to the scope of the COS to be involved in its development	Raise awareness of COS among clinical trialists Increase engagement with clinical trialists Ensure outcomes important to clinical trialists are included in the COS
	Involve patients in the development of COS	Ensure outcomes important to patients are included in the COS
	Consider the impact of collecting the outcomes on patients	Reduce patient burden of COS
	Develop a dissemination plan including website, publication, social media, conferences	Raise awareness of COS among clinical trialists
	Recommend outcome measurement instruments as well as outcomes	Improve consistency in how outcomes are measured Tackle uncertainly around which outcome measurement instruments to use Make improvements to outcome measurement instruments
	Engage with individuals in the research community who are committed to the longevity of the COS	Increase likelihood of COS being completed and maintained

	Determine if a COS is needed prior to starting the development process	Ensures necessity and suitability of COS for the clinical area
COS organisations	Deliver information about COS in educational programmes	Raise awareness of COS among clinical trialists Increase knowledge of COS and their purpose Facilitate understanding of how to apply COS
	Develop guidelines on assessing the relevance and applicability of COS	Assist CIs in assessing the relevance and applicability of COS for a particular RCT
	Liaise with funders over lack of funding to fully develop COS	Facilitate a source of funding to enable the completion of COS
	Provide structure to the process of updating COS	Encourage regular reviews and appropriate updates of COS
Funders	Recommend the use of COS in application forms	Raise awareness
	Feedback to applicants about COS	Support clinical trialists to implement COS

Chapter 6: Discussion and future work

6.1 Summary of main findings

COS seek to address problems with outcomes in RCTs by improving consistency, reducing outcome reporting bias and ensuring that outcomes important to patients are measured. By improving the selection and reporting of outcomes in RCTs, COS have the potential to improve the quality of research and reduce research waste. However, this reduction in waste will only be realised through the implementation of COS. This thesis presents an investigation of methods to assess and improve the uptake of COS in RCTs. The specific aims were to:

- Explore the extent to which COS are used in RCTs across different areas of health
- Investigate citation analysis as an efficient method to assess COS uptake in RCTs
- Assess the impact that a funder of RCTs may have on COS uptake
- Explore the barriers and facilitators to COS uptake by clinical trialists

The systematic review reported in Chapter 2 established that few studies had assessed COS uptake. Twenty-four studies that had focused on uptake in RCTs and two studies that had focused on uptake in systematic reviews were identified. These studies reported uptake for a total of 17/337 COS from five of 31 disease categories for which COS have been developed. The rates of uptake reported varied from 0% (chronic gout, after eight years) (66) to 82% (rheumatoid arthritis, after 13 years) (63) of RCTs and 10% (chronic pain) (71) of systematic reviews that had measured the full COS. Variation was also found in the uptake rate of individual outcomes in studies that had assessed the uptake of each outcome recommended by the COS (58-62, 64-74, 76, 77, 80, 81, 83). A facilitator to uptake that was suggested following an assessment of the implementation of the rheumatoid arthritis COS was endorsement of the COS by drug regulatory authorities (75). Suggested barriers to uptake included poor awareness of COS (58, 72, 73, 76, 83), a lack of validated outcome measurement instruments for the recommended outcomes (58, 72, 73, 76), limited stakeholder involvement in the development of the COS (58, 59, 63, 72, 81, 83), poor understanding of COS amongst trialists (64, 76), patient burden (68), cost (79) and lack of standardised recommendations across regulatory agencies (81).

The systematic review highlighted the need for a method to assess COS uptake that was less resource-intensive than those used previously which had involved the lengthy process of

identifying and examining reports of RCTs. Chapter 3 explored whether the number of citations received by a COS publication would give an indication as to the uptake of the COS, removing the need to examine RCT reports. Although the process to obtain the number of citations received by a COS was efficient, the citation count alone did not provide reliable evidence of its uptake. The study found that the citations received by COS publications came from different types of articles with RCT reports accounting for a small proportion. When an RCT report does cite a COS publication, it does not necessarily mean that the COS was implemented. Furthermore, some RCTs measure a COS but do not cite the COS publication in their report. Even if all of the articles that had cited a COS publication were reports of RCTs that had used the COS, and all RCTs that had used the COS cited it in their report, without knowing the total number of RCTs that had been conducted it is not possible to determine the proportion of RCTs that measured the COS. Therefore, citation analysis is not recommended as an approach to assess uptake of COS. A more reliable method of COS uptake assessment that is less resource-intensive than those used previously examines the information recorded about outcomes in a clinical trial registry and is currently the recommended method to assess COS uptake (78).

The low rates of COS uptake found by the studies identified in the systematic review reported in Chapter 2 indicated that interventions to improve the uptake of COS are needed. One strategy already in place is for funders of RCTs to recommend that their applicants consider a COS for their study. Chapter 4 reports an assessment of the impact of such a recommendation by the NIHR HTA. The findings showed that a funder can have an impact on COS uptake with 17/95 (18%) applicants specifically stating that they had searched the COMET database which is recommended by the funder. A further 19 applicants also stated that they searched for a COS using other sources. However, a search of the COMET Initiative database found that a completed, published COS existed for 24 of the applications at the time of their submission but only seven (29%) of those applications referred to the relevant COS. Furthermore, it is possible that more applicants may have considered a COS but not mentioned this in their application, perhaps in cases where they did not find a COS that was relevant for their study. Therefore, we suggest further steps, detailed in Section 6.3, that could be taken by a funder to increase the impact of their recommendation to consider a COS.

In order to inform the identification and development of further interventions to improve the uptake of COS, qualitative interviews were carried out with a purposive sample of CIs for NIHR HTA-funded RCTs as reported in Chapter 5. By applying the BCW framework, a theory-based approach was taken to identify the most appropriate interventions to improve COS uptake. The interviews identified barriers and facilitators relating to the behaviour of CIs that could be addressed by behaviour change interventions. These included awareness of COS and understanding of the need for COS. Some barriers and facilitators related to the characteristics of COS and could be addressed by COS developers. These included patient burden and engagement with clinical trialists. Other barriers and facilitators related to the wider research system, such as support from funders and journals to use COS.

6.2 Dissemination of thesis findings

The studies presented in Chapters 2, 3, and 4 have been disseminated through publication in journals (56, 84, 113) and presentation at international conferences (146-148). In addition, the review of NIHR HTA funding applications described in Chapter 4 has been presented to the Ensuring Value in Research (EViR) Funders' Forum during their 2020 virtual conference and in an NIHR all-staff seminar. Feedback from the seminar was that the results were encouraging given that new guidance typically takes time to start to filter through to applications. The seminar was followed by a round table discussion with representatives of NIHR where it was agreed that an update of this study should be carried out to assess applications submitted between 2016 and 2019. Further details of this update are presented in Section 6.4. The qualitative interview study reported in Chapter 5 will be submitted for publication and conference presentation.

All participants who responded to the survey in Chapter 4 and took part in the interviews in Chapter 5 were asked if they would like to receive a copy of the study report and these will be provided where requested.

Three of my supervisors are members of the COMET Initiative and as such provide a direct link to disseminate the findings to the COS developers, funders and regulators that they have connections with. The findings have been disseminated via the COMET Initiative Twitter account and newsletters, and will be listed in the COMET Handbook update scheduled for 2022.

6.3 Implications

Based on the findings of this thesis, recommendations are suggested to improve the uptake of COS. These recommendations are aimed at COS developers, organisations in the wider research system and organisations that promote the development and uptake of COS.

6.3.1 COS developers

The findings indicate that there are steps that COS developers can take to improve uptake of their COS.

- ***Establishing the necessity and suitability of a COS***

The interview study findings suggest that more work could usefully be carried out at the start of the COS development process to ascertain the necessity and suitability of a COS. This could help to avoid the development of COS that will not be implemented. The COMET Initiative Handbook (17) recommends investigation into the selection and reporting of outcomes in the clinical area, by carrying out a systematic review, which may help to decide whether a COS is needed. It would also be prudent to engage with trialists who would use the COS at this early stage to explore their views on whether a COS would be appropriate and, if developed, implemented. An example of this can be taken from a COS that was developed for dementia to be used in clinical practice. The developers began by carrying out a systematic review of outcomes which they concluded confirmed the need for a COS (149). Prior to starting the consensus process to develop the COS they then interviewed health professionals about the proposed COS and found that there was support for its development (150). In addition, the health professionals interviewed explained that as well as recommending outcomes, they would like low cost and easy to use measurement instruments to be presented as a "toolkit" that should include details of how and when to use the instruments. This information could be used to inform the development of the COS to ensure its use. The interviewees in the dementia COS study also specified how the COS should be disseminated for maximum impact, helping the COS developers to draft a dissemination plan.

If COS developers also consider whether a suitable COS already exists in the area prior to developing a new one, difficulties for trialists in deciding which COS to use could be avoided. For example, following a proposal to develop a COS for discourse in aphasia (151), Wallace

et al., who had previously developed a COS for aphasia, suggested that attention be paid to improving discourse outcome measurement instruments so that they could be included in the existing aphasia COS rather than developing an additional COS (152). Furthermore, if COS developers consider the barriers that have impeded uptake in previous COS, they can plan strategies to address these barriers prior to and during development.

- ***Engaging with trialists who will use the COS***

As suggested above, we recommend engaging with trialists at the start of the COS development process, but also recommend that this engagement continues throughout each subsequent step. In the interview study CIs highlighted a lack of engagement as a barrier to them using a COS. Whilst recommendations already exist to include clinical trialists in COS development (19), interviewees pointed out that this should include representatives of all clinical roles and all specialties of those who would conduct relevant RCTs. For example, a COS for all treatments for osteoarthritis might be relevant to RCTs carried out by rheumatologists, orthopaedic surgeons and physiotherapists. It is therefore important that COS developers consider who the COS might be used by when defining its scope and ensure full inclusion of stakeholders in its development.

- ***Considering patient burden***

As well as engaging with those who will use the COS in research, it is important that patients who have experience of the condition are involved in the development of the COS. Patient involvement is already recommended for COS development to ensure that the outcomes important to patients are included (20). Involving patients can also help when considering patient burden, another barrier to uptake referred to by CIs. Involving patients in discussions around the choice of outcomes and outcome measurement instruments to be recommended by the COS will help in ascertaining the burden that might be placed on patients to complete the assessments.

- ***Recommending outcome measurement instruments***

A further barrier to uptake of COS identified in the interview study was the lack of recommendations for outcome measurement instruments. In a recent systematic review of the methods used by COS developers to select outcome measurement instruments, Gorst et al. found that only 118 (35%) of the 337 published COS studies had recommended instruments (145). We therefore recommend that once the COS outcomes have been

decided, developers move on to deciding outcome measurement instruments. As well as increasing standardisation across studies, these recommendations will help trialists in deciding which instruments to use. Where an appropriate outcome measurement instrument does not exist, COS developers have an opportunity to start a research agenda to address this, thus improving the instruments available to trialists. As mentioned in previous chapters, guidance has been produced by COMET and COSMIN to aid COS developers in choosing outcome measurement instruments for their COS (86).

- ***COS dissemination***

Based on responses from CIs, we recommend that COS developers disseminate their COS through a variety of channels. Alongside publication, COS developers could increase awareness of their COS through social media, creation of a website and presentation at conferences. As with the COS for dementia in practice referenced above (150), COS developers could ask the intended users of the COS how they would like to be notified of its development.

- ***Monitoring and updating COS***

The importance of ensuring that the recommendations of a COS remain current was highlighted by CIs in the interview study. There were concerns that a COS could become out of date following advances in technology and outcome measurement instruments alongside changes to patients' priorities. One issue that arises in the practicalities of updating a COS is that the original developers may have moved on to other projects and do not have the capacity to commit to an update. To address this issue COS developers should aim to include in their team individuals who are invested in the clinical area and therefore have an interest in maintaining the COS over time. Currently there is no guidance on how long after the development of a COS an update should be considered, or how often. Further work is needed to address these issues, alongside the process for updating a COS. This is discussed in more detail in Section 6.4.

6.3.2 Wider research system

- ***Regulatory authorities***

The systematic review of COS uptake studies showed that the COS for rheumatoid arthritis developed through the WHO and ILAR stood out from the others assessed by having consistently high levels of uptake in RCTs (63, 75, 78, 79). The key difference between this

COS and the others assessed is that it has been endorsed by the EMA and FDA. In one of the studies assessing the uptake of this COS, the authors noted an increase in uptake following endorsement by the regulators (75) suggesting that support from regulatory authorities can improve COS uptake. The COMET Initiative is currently exploring whether the outcomes recommended by COS align with those in FDA and EMA guidance in other clinical areas (153). This has been undertaken already for the COS for type 2 diabetes and good alignment was found (154). Exploring this for other COS may open discussions between COMET and regulators about support for COS in regulatory guidance.

- ***Funders***

Several funders of RCTs currently recommend that their applicants consider a COS for their study, including NIHR HTA (UK), Health Research Board (Ireland), Deutsche Forschungsgemeinschaft (Germany), Belgian Health Care Knowledge Centre and Patient-Centered Outcomes Research Institute (USA). The assessment of the extent to which applicants follow this guidance from the NIHR HTA found that such recommendations can have an impact on uptake. To further increase this impact, we recommend that the advice to consider COS is not only included in the guidance provided to applicants but also in the application form itself where it would be more prominent. We also suggest that funders ask applicants to state whether or not they searched for a COS, giving details of what they found. As well as providing further encouragement to applicants to search for a COS, this will allow an accurate assessment of whether applicants are following the advice. In addition to providing a recommendation in guidance documents and application forms, we recommend that funding panels carry out their own check for a COS during their consideration of the application where there is no evidence that a COS has been considered. If a relevant COS is found this will enable the panel to recommend consideration of the COS in their feedback.

6.3.3 Organisations that promote the development and uptake of COS

- ***Educational programmes***

Although experienced CIs who participated in the interview study demonstrated an awareness of COS and understanding of their purpose, one interviewee who was a CI for the first time had not heard of COS. Furthermore, interviews indicated that some trialists do not understand that COS outcomes are recommended as a minimum and some interviewees were concerned important outcomes might be excluded from an RCT if these are not included in a COS. To improve awareness, knowledge and understanding of COS we

recommend that organisations involved in the promotion of COS consider providing educational programmes. These could be in the form of standalone workshops that focus on COS such as the one presented by the COMET Initiative at the International Clinical Trials Methodology Conference (ICTMC) 2019 (155), or as part of existing relevant education courses such as those delivered for Continuing Professional Development.

- ***Guidelines for assessing suitability of COS***

In the interview study, CIs expressed concerns that a COS might be used without first assessing its suitability for the particular RCT. These concerns were in relation to the quality of the COS and its relevance for the RCT. The COS-STAD guidance, which provides COS developers with the minimum standards for the development of COS, can guide trialists in assessing whether the methods used to develop a COS are suitable (19). Assessing the relevance of a COS may not be straightforward in cases where there is more than one COS for the same condition or a COS is a partial match for the RCT in terms of the scope. Currently, no guidance exists to help trialists to make decisions about the suitability of COS in these circumstances and further work is needed to develop such guidance. This is discussed in more detail in Section 6.4.

6.4 Future work

6.4.1 Impact of funder recommendations to use COS

The review of NIHR HTA funding applications reported in Chapter 4 concluded that funders can have an impact on COS uptake by recommending to their applicants that they consider using a COS where one exists. As noted in Chapter 4, it will likely take time for trialists to become accustomed to the process of searching for and implementing COS. It would therefore be useful to undertake an update of this review by evaluating more recent applications and comparing the results to the 2012-2015 assessment which can be used as a baseline. This would give an up to date impression of whether COS are being considered and whether this has improved over time. Following discussions with representatives from NIHR, it has been agreed that this study should go ahead by assessing applications submitted between January 2016 and December 2019.

As in the original study, all applications for RCT funding submitted to the NIHR HTA researcher-led workstream will be identified, including those that did not go on to receive

funding, this time for the period January 2016 – December 2019. Sections of the application form and the detailed project description of each identified NIHR HTA application will be examined and the following information extracted:

- Evidence that the COMET database had been searched to establish whether or not a COS exists
- Any reference to a COS study published in the COMET database
- Evidence that a COS was included in the application, if one exists.
- Reasons given by an applicant for not including a COS where one exists
- Any information included about the COMET database and/or COS in general

The study team will review the COMET database for the clinical area to confirm the existence or not of relevant COS.

Following the assessment of application forms and detailed project descriptions a survey will be sent to all applicants to further investigate the researcher's decision to search for and use a COS or not and to discover more about their strategies for selecting outcomes.

Following extraction of the data the following analysis will be performed:

- Assessment of the number of NIHR HTA applications referencing the COMET database or a COS published in the COMET database
- Assessment of the number of NIHR HTA applications using a COS, if one exists
- Number of applications that could have used a COS based on a review of the COMET database

These assessments will be compared to those carried out in the original 2012-2016 study to draw conclusions about the influence over time of a funder recommending the use of a COS.

A limitation of the study reported in Chapter 4 was that the assessment of funding applications was restricted to one funder in the UK. In order to obtain a wider view of the influence of funder recommendations on COS uptake it is necessary to carry out assessments of other funders outside of the UK. Currently, funders based in Ireland, Germany, Belgium and the USA recommend COS to their applicants (Table 12).

Table 12: Funders recommending COS to their applicants

Country	Funder
Ireland	Health Research Board (HRB)
Germany	Deutsche Forschungsgemeinschaft (DFG)
Belgium	Belgian Health Care Knowledge Centre (KCE)
USA	Patient-Centered Outcomes Research Institute (PCORI)

KCE and DFG have carried out preliminary assessments of whether their applicants followed the recommendation about searching for a COS. KCE examined 38 research outlines of investigator-led applications submitted in 2018 and 2019. They found that 13% of applicants had mentioned that they had searched for a COS. DFG examined study registrations and published study protocols between 2017 and February 2020 for any mention of a COS. Of 32 RCTs they did not find any that had used a COS, though a relevant COS was listed in the COMET database for 14 of the RCTs.

Discussions have taken place with HRB and PCORI about reviewing their funding applications to assess the impact of their recommendations. Both funders plan to carry out such assessments in collaboration with the COMET Initiative.

6.4.2 Barriers to COS uptake outside of the UK

The qualitative interview study reported in Chapter 5 explored the barriers and facilitators to COS uptake by CIs of RCTs. A limitation of this study was that participation in the interviews was limited to CIs based in the UK. The rationale for this was that CIs based in the UK are more likely to be aware of COS through the work of the UK-based COMET Initiative and a UK-based funder (NIHR) recommends using COS to their applicants. However, further work is needed to investigate the barriers and facilitators to COS uptake beyond the UK with a particular focus on:

- Awareness of COS
- Understanding of COS and their benefits
- Support from funders to use COS
- Importance of international participation in COS development
- Global relevance of outcomes recommended by COS

- Transferability of outcome measurement instruments recommended by COS

Such interviews with CIs outside of the UK may highlight different barriers and facilitators to COS uptake and therefore different types of intervention to improve uptake.

6.4.3 COS publications

Suggestions for dissemination have been made based on the ways in which CIs became aware of COS as discussed in the interview study. A popular dissemination strategy is publication of COS in a journal. The assessment of citation analysis reported in Chapter 3 raised a hypothesis about whether how a COS is presented in a journal affects its uptake. The COS publications included in that study either focused on outcomes only and the dissemination of the COS or they made recommendations about outcomes whilst addressing other RCT design issues, such as patient inclusion criteria. The findings suggest that while a publication focusing on several design issues is more likely to be cited, uptake of a COS is more likely when the COS is the sole focus of the publication. This may be because the recommendations about outcomes are missed in publications that make other design recommendations or the author citing the COS publication might have been looking for advice about a particular design issue and overlooked the other recommendations made in the publication. Using a clinical trial registry as an efficient way of assessing whether outcomes in a COS will be included in an RCT, it is possible to compare uptake based on how the COS was reported in a publication. Furthermore, it would be of interest to explore whether there are any differences in uptake of COS depending on the type of journal that COS developers choose to publish their COS in. For example, some COS are published in disease specific journals, such as the International Dental Journal, whilst other are published in journals that cover research from any discipline within science and medicine, such as PLOS One. Assessing differences in uptake depending on journal type could lead to recommendations about how developers should endeavour to publish their COS.

6.4.4 Development of guidance

Updating COS

The systematic review reported in Chapter 2 demonstrated variability in the uptake of individual outcomes recommended by a COS. Where assessment of a COS reveals that certain outcomes are not being measured, a review and revision of the COS may be necessary. Concerns about COS becoming out of date was also identified as a barrier to

uptake in the interview study. As mentioned in Section 6.3, there is currently no guidance to support the updating of a COS. The development of guidance could facilitate more updates to ensure that COS remain current thus improving uptake. It would be helpful for guidance to include information about:

- The criteria for deciding that an update is required
- The process for updating a COS, i.e. whether the same process for the initial development of a COS should be followed
- Who should be responsible for updating a COS

Deciding who should update a COS and the criteria on which to base the update could be particularly difficult issues to address. As pointed out by a CI in the interview study, difficulties may arise when a group who were not involved in the initial development process decide that an update should be carried out. To address these issues, the CI suggested having a structure in place, perhaps overseen by the COMET Initiative, where suggested updates are submitted and go ahead only with approval.

Assessing relevance of COS

Alongside updating COS, there is currently no guidance to help trialists with assessing the relevance of a COS. Guidance around COS suitability would be helpful to advise trialists on the things to consider when establishing whether a COS matches the scope of their RCT. Further guidance would also be helpful for situations where there is more than one COS for the same condition or a COS is a partial match in terms of scope for the RCT.

6.4.5 Barriers and facilitators to uptake of COS in systematic reviews

The focus of this thesis was uptake of COS in RCTs, but COS are also recommended for use in systematic reviews (156). Surveys carried out to garner the opinion of Co-ordinating Editors of Cochrane Review Groups found support for the use of COS in systematic reviews (157, 158). However, the systematic review of COS uptake reported in Chapter 2 identified two studies that had assessed uptake of COS in systematic reviews. The study that reported the proportion of systematic reviews that had assessed the full COS found that 10% of the reviews had included the COS. Both studies had assessed uptake of individual outcomes recommended by the COS and found variability in their uptake. To build on the previous surveys, qualitative interviews would enable in-depth exploration of the barriers and facilitators to uptake, which may differ to those that affect trialists' use of COS.

6.5 Final summary

COS have the potential to reduce research waste created by the poor selection and reporting of outcomes in RCTs. However, this potential will only be realised through the uptake of COS in RCTs. The work reported in this thesis identified the need for interventions to improve COS uptake. Through the assessment of an existing intervention by trial funders, and the exploration of barriers and facilitators to COS uptake, recommendations have been made as to ways in which uptake can be improved.

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Appendices

Appendix 1: Publications

Chapter 2

Hughes KL, Clarke M, Williamson PR. A systematic review finds core outcome set uptake varies widely across different areas of health. Journal of Clinical Epidemiology. 2021; 129: 114-123. doi.org/10.1016/j.jclinepi.2020.09.029

Chapter 3

Barnes, KL, Kirkham, JJ, Clarke, M, & Williamson, PR. Citation analysis did not provide a reliable assessment of core outcome set uptake. Journal of Clinical Epidemiology. 2017; 86: 153–159. doi.org/10.1016/j.jclinepi.2017.03.003

Chapter 4

Hughes KL, Kirkham JJ, Clarke M, Williamson PR. Assessing the impact of a research funder's recommendation to consider core outcome sets. PLoS ONE. 2019; 14(9): e0222418. doi.org/10.1371/journal.pone.0222418

Appendix 2: References of COS publications included in citation analysis for systematic review of COS uptake (Chapter 2)

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Benedetto U, editor. PLoS One. 2015;10:e0122204
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336. Howell M, Wong G, Turner RM, et al. The consistency and reporting of quality-of-life outcomes in trials of immunosuppressive agents in kidney transplantation: a systematic review and meta-analysis. Am J Kidney Dis. 2016;67:762-774
337. Acar C, Kleinjan GH, van den Berg NS, et al. Advances in sentinel node dissection in prostate cancer from a technical perspective. Int J Urol. 2015;22:898-909

Appendix 3: Key words to identify studies of COS uptake for systematic review of COS uptake (Chapter 2)

For COS:
core
outcome(s)
endpoint(s)
measure(s)
measurement(s)
data(set)
set(s)
standardis/ze(d)(ing)(ation)
domain(s)
common

For uptake:
strategy(ies)
assess(ed)(ing)(ment/s)
implement(ed)(ation)(ing)
consensus
appropriate(ness)(ly)
recommend(ed)(ation/s)(ing)
challenge(s)
obstacle(s)
barrier(s)
faciliate(s)(ion)(ors)(ed)(ing)
adopt(ion)(ing)(ed)
uptake

Appendix 4: COS uptake studies included in systematic review (Chapter 2)

A1. Uptake study:
van der Heide A, Jacobs JWG, Dinant HJ, Bijlsma JWJ. The impact of endpoint measures in rheumatoid arthritis clinical trials. Seminars in Arthritis and Rheumatism 1992;21(5):287-94.

COS assessed:
Scott DL, Spector TD, Pullar T, McConkey B. What should we hope to achieve when treating rheumatoid arthritis? Annals of the Rheumatic Diseases 1989;48(3):256-61.

Bombardier C, Tugwell P, Sinclair A, Dok C, et al. Preference for endpoint measures in clinical trials: results of structured workshops. Journal of Rheumatology 1982;9(5):798-801.

A2. Uptake study:
Kalyoncu U, Dougados M, Gossec L, Daurès JP. Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: A systematic literature review. Annals of the Rheumatic Diseases 2009;68(2):183-90.

COS assessed:
Boers M, Tugwell P, Felson DT, Van Riel PLCM, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. Journal of Rheumatology 1994;21(SUPPL. 41):86-9

A3. Uptake study:
Beale M, Cella M, de C. Williams AC. Comparing patients' and clinician-researchers' outcome choice for psychological treatment of chronic pain. Pain 2011;152(10):2283-6.

COS assessed:
Turk DC, Dworkin RH, Revicki D, Harding G, Burke LB, Cella D, Cleeland CS, Cowan P, Farrar JT, Hertz S, Max MB, Rappaport BA. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. Pain 2008;137:276–85.

A4. Uptake study:
Palominos PE, Gaujoux-Viala C, Fautrel B, Dougados M, et al. Clinical outcomes in psoriatic arthritis: A systematic literature review. Arthritis Care & Research 2012;64(3):397-406.

COS assessed:
Gladman DD, Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol 2007;34:1167–70.

A5. Uptake study:
Marks M, Schoones JW, Kolling C, Herren DB, et al. Outcome measures and their measurement properties for trapeziometacarpal osteoarthritis: a systematic literature review. 2013. p. 822-38.

COS assessed:

Bellamy N, Kirwan J, Boers M et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997, 24: 799–802.

A6. Uptake study:
Kirkham JJ, Boers M, Tugwell P, Clarke M, et al. Outcome measures in rheumatoid arthritis randomised trials over the last 50 years. Trials 2013;14(1).

COS assessed:
Boers M, Tugwell P, Felson DT, Van Riel PLCM, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. Journal of Rheumatology 1994;21(SUPPL. 41):86-9

A7. Uptake study:
Bautista-Molano W, Navarro-Compán V, Landewé RBM, Boers M, et al. How well are the ASAS/OMERACT core outcome sets for ankylosing spondylitis implemented in randomized clinical trials? A systematic literature review. Clinical Rheumatology 2014;33(9):1313-22.

COS assessed:
van der Heijde D, Bellamy N, Calin A et al (1997) Preliminary core sets for endpoints in ankylosing spondylitis. J Rheumatol 24:2225–9

A8. Uptake study:
Dalbeth N, Zhong CS, Grainger R. Outcome Measures in Acute Gout: A Systematic Literature Review. 2014, (3), p. 558.

COS assessed:
Schumacher HR, Taylor W, Edwards L, Grainger R, Schlesinger N, Dalbeth N, et al. Outcome domains for studies of acute and chronic gout. J Rheumatol. 2009; 36:2342–5.

A9. Uptake study:
Hann KEJ, McCracken LM. A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy. Journal of Contextual Behavioral Science 2014;3(4):217-27.

COS assessed:
Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003; 106:337–45.

A10. Uptake study:
Mulla SM, Maqbool A, Sivananthan L, Lopes LC, et al. Reporting of IMMPACT-recommended core outcome domains among trials assessing opioids for chronic non-cancer pain. Pain 2015;156(9):1615-9.

COS assessed:
Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003; 106:337–45.

Turk DC, Dworkin RH, Revicki D, Harding G, Burke LB, Cella D, Cleeland CS, Cowan P, Farrar JT, Hertz S. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. PAIN 2008;137:276–85.

A11. Uptake study:
Araújo F, Cordeiro I, Ramiro S, Falzon L, et al. Outcomes assessed in trials of gout and accordance with OMERACT-proposed domains: a systematic literature review. Rheumatology (Oxford, England) 2015;54(6):981-93.

COS assessed:
Schumacher R, Edwards L, Perez-Ruiz F et al. Outcome measures for acute and chronic gout. J Rheumatol 2005;32:2452-5.

A12. Uptake study:
Pruppers MHJ, Draak THP, Faber CG, Merkies ISJ, et al. Outcome measures in MMN revisited: Further improvement needed. Journal of the Peripheral Nervous System 2015;20(3):306-18.

COS assessed:
Merkies IS, Lauria G (2006). 131st ENMC International workshop: selection of outcome measures for peripheral neuropathy clinical trials 10–12 December 2004, Naarden, The Netherlands.
Neuromuscul Disord 16:149–156.

A13. Uptake study:
Kalyoncu U, Ogdie A, Campbell W, Bingham CO, et al. Systematic literature review of domains assessed in psoriatic arthritis to inform the update of the psoriatic arthritis core domain set. BMJ Publishing Group; 2016.

COS assessed:
Gladman DD, Mease PJ, Strand V, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol 2007;34:1167–70.

A14. Uptake study:
Copsey B, Hopewell S, Becker C, Cameron ID, et al. Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: A case study in fall injury prevention. Trials 2016;17(1).

COS assessed:
Lamb SE, Jørstad‐Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc. 2005;53(9):1618‐22.

A15. Uptake study:
Stothers L, Nigro M, Tsang B, Lazare D, et al. An integrative review of standardized clinical evaluation tool utilization in anticholinergic drug trials for neurogenic lower urinary tract dysfunction. Spinal Cord 2016;54(12):1114-20.

COS assessed:

Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Ditunno JF et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord 2007; 45: 206–221.

A16. Uptake study:
Lange T, Rataj E, Kopkow C, Lützner J, et al. Outcome Assessment in Total Knee Arthroplasty: A Systematic Review and Critical Appraisal. Journal of Arthroplasty 2017;32(2):653-65.e1.

COS assessed:
Bellamy N, Kirwan J, Boers M et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997, 24: 799–802.

A17. Uptake study:
Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. BMJ (Clinical Research Ed.) 2017;357:j2262-j.

COS assessed:
Boers M, Tugwell P, Felson DT, Van Riel PLCM, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. Journal of Rheumatology 1994;21(SUPPL. 41):86-9

A18. Uptake study:
Boric K, Jelicic Kadic A, Boric M, Zarandi-Nowroozi M, et al. Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents. European Journal of Pain 2018.

COS assessed:
McGrath, P. J., Walco, G. A., et al. (2008). "Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations." Journal of Pain 9(9): 771-783

A19. Uptake study:
Dosenovic S, Kadic AJ, Jeric M, Boric M, et al. Efficacy and Safety Outcome Domains and Outcome Measures in Systematic Reviews of Neuropathic Pain Conditions. 2018. p. 674-84.

COS assessed:
Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003; 106:337–45.

A20. Uptake study:
Boric K, Dosenovic S, Kadic AJ, Boric M, et al. Efficacy and Safety Outcomes in Systematic Reviews of Interventions for Postoperative Pain in Children: Comparison Against the Recommended Core Outcome Set. 2018. p. 2316-21.

COS assessed:

McGrath, P. J., Walco, G. A., et al. (2008). "Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations." Journal of Pain 9(9): 771-783

A21. Uptake study:

Farag AM, Albuquerque R, Ariyawardana A, Chmieliauskaite M, et al. World Workshop in Oral Medicine VII: Reporting of IMMPACT-recommended outcome domains in randomized controlled trials of burning mouth syndrome: A systematic review. Oral Diseases 2019(S1):122.

COS assessed:

Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003; 106:337–45.

A22. Uptake study:

Kirkham JJ, Bracken M, Hind L, Pennington K, et al. Industry funding was associated with increased use of core outcome sets. 2019. p. 90-7.

COS assessed:

Boers M, Tugwell P, Felson DT, Van Riel PLCM, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. Journal of Rheumatology 1994;21(SUPPL. 41):86-9

A23. Uptake study:

Smith TO, Arden NK, Mansfield M, Hawker GA, et al. Uptake of the OMERACT-OARSI hip and knee osteoarthritis core outcome set: Review of randomized controlled trials from 1997 to 2017. Journal of Rheumatology 2019;46(8):976-80.

COS assessed:

Bellamy N, Kirwan J, Boers M et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997, 24: 799–802.

A24. Uptake study:

Smith TO, Collier T, Sheehan KJ, Sherrington C. uptake of the hip fracture core outcome set: analysis of 20 years of hip fracture trials. Age & Ageing 2019;48(4):595-8.

COS assessed:

Haywood KL, Griffin XL, Achten J, Costa ML. Developing a core outcome set for hip fracture trials. Bone Joint J 2014; 96-B: 1016 –23.

A25. Uptake study:

Krsticevic M, Boric K, Dosenovic S, Dimcea DAM, et al. Outcome domains, outcome measures, and characteristics of randomized controlled trials testing nonsurgical interventions for osteoarthritis. Journal of Rheumatology 2020;47(1):126-31.

COS assessed:

Bellamy N, Kirwan J, Boers M et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997, 24: 799–802.

A26. Uptake study:
Vincent R, Chalmers JR, McWilliams C, Thomas KS, et al. Assessing uptake of the Harmonising Outcome Measures for Eczema (HOME) Core Outcome Set and Recommended Instruments. The British journal of dermatology 2020.

COS assessed:
Schmitt J, Spuls P, Boers M, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. Allergy 2012; 67:1111–1117.

Appendix 5: Characteristics of COS selected to assess citation analysis as an approach to COS uptake assessment (Chapter 3)

		Scope of COS			Development		
	COS only or wider trial design issues	**Population**	**Intervention**	**Intended use**	**Method(s)**	**Participants**	**Location**
Systemic Sclerosis (SSc)							
White 1995	Wider trial design issues	Patients with diffuse cutaneous SSc of less than 24 months' duration	Not specified	Phase III trials of disease-modifying interventions in SSc.	A committee analysed published and unpublished data and opinions from experts	Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the Council on Research of the American College of Rheumatology	North America
Outcomes	14 (death or survival time, weight or BMI, health status, physician global status, patient global status, serum creatinine, blood pressure, forced vital capacity, carbon monoxide diffusing capacity, left ventricle ejection fraction, serious arrhythmia requiring therapy, pseudo obstruction, malabsorption requiring total parenteral nutrition, skin score)						
Khanna 2008	COS only	Not specified	Not specified	Observational and multi-centre clinical trials in SSc	3-round Delphi exercise and nominal group technique	Scleroderma Clinical Trials Consortium membership	North America, Europe, Asia, South America, Australia
Outcomes	11 Domains, 31 parameters: **Skin**: Modified Rodnan skin score (range 0–51), Visual analogue scale (VAS)/Likert score of patient's global assessment for skin activity, VAS/Likert score of doctor's global assessment for skin activity, Durometer. **Musculoskeletal**: Tender joint count, Tendon friction rubs assessed by the doctor, Serum creatinine phosphokinase aldolase. **Cardiac**: Cardiac echocardiogram with Doppler, Right heart catheterisation, 6-min walk test, Borg dyspnoea instrument. **Pulmonary**: Pulmonary function testing, Validated measure of dyspnoea, Breathing VAS from the Scleroderma Health Assessment Questionnaire (S-HAQ), High resolution computer tomography (HRCT) of the lungs: quantifiable scale. **Renal:** Calculated creatinine clearance based on serum creatinine (Cockroft–Gault or Modification of Diet in Renal Disease (MDRD) formula), Pre-defined renal crisis (presence or absence). **Gastrointestina**l: Body mass index (BMI), Validated gastrointestinal (GI) tract VAS scale (part of S-HAQ) or other SSc-validated GI questionnaire. **Health-related quality of life and function**: Health Assessment Questionnaire-Disability Index (HAQ-DI), VAS pain from the HAQ-DI, Short form-36 (SF-36) version 2. **Global health**: VAS/Likert patient global severity,						

	VAS/Likert doctor global severity, Scleroderma-related health transition by patient, Scleroderma-related health transition by doctor. **Raynaud phenomenon**: Raynaud condition score, VAS Raynaud (part of S-HAQ). **Digital ulcers**: Active digital tip ulcer count on the volar surface, VAS digital ulcer (part of S-HAQ). **Biomarkers**: Acute phase reactant(s): erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).						
Rheumatoid Arthritis							
Bombardier 1982	COS only	Not specified	Not specified	Clinical trials	Nominal group technique	Rheumatologists, representatives of rheumatological societies, nurses, physiotherapists, researchers	North America
Outcomes	11 (Joint count, pain relief, global assessment of change in disease activity, pain (patient related), global assessment of disease activity, morning stiffness, grip strength, self-care, physical activity/inability, pain (function), role activity)						
Scott 1989	COS only	Not specified	Slow acting anti rheumatic drugs	Clinical trials and individual patient management (practice)	Consensus meeting	15 rheumatological workers from nine centres with special interests in the area of disease assessment	Europe
Outcomes	5 (Mortality, morbidity assessment, functional index, drug reaction index, clinical and laboratory indices of disease activity)						
van Riel 1992	COS only	Not specified	Not specified	All international clinical trials	Results of study of the validity of 10 frequently used single variables and data from the literature	EULAR Standing Committee for International Clinical Studies	Europe
Outcomes	7 (Number of tender joints, number of swollen joints, pain score, patient global score, C-reactive protein or erythrocyte sedimentation rate (ESR), health assessment, Larsen radiographic score)						
Felson 1993	COS only	Not specified	All interventions	All rheumatoid	Literature review, nominal group technique,	Experts in clinical trials and health services research, conference participants	North America, Europe

				arthritis clinical trials	international conference		
Outcomes	8 (Tender joint count, swollen joint count, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, patient's assessment of pain, laboratory evaluation of 1 acute-phase reactant, radiography or other imaging technique for trials lasting at least one year)						
Fried 1993	COS only	Not specified	Not specified	Rheumatoid arthritis clinical trials	Nominal group technique at international conference	Conference participants	North America, Europe
Outcomes	8 (Tender joint count, swollen joint count, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, patient's assessment of pain, laboratory evaluation of 1 acute-phase reactant, radiography or other imaging technique for trials lasting at least one year)						
Tugwell 1993	COS only	Not specified	Slow acting agents, nonsteroidal antiinflammatory drugs (NSAID), nonpharmacologic interventions	Rheumatoid arthritis clinical trials	Nominal group technique, plenary session with voting	Conference participants	North America, Europe, Australia
Outcomes	8 (joint pain/tenderness, joint swelling, pain, patient global assessment, physician global assessment, disability, acute phase reactants, radiographs for studies of one year or longer)						
Boers 1994	COS only	Not specified	Antirheumatic drugs	Rheumatoid arthritis clinical trials	Direct questioning, rating of sample profiles of patients and trials, interactive voting and discussion	Conference participants (rheumatologists, methodologists, drug regulatory officials, pharmaceutical physicians)	North America, Europe, Australia

Outcomes	8 (pain, patient global assessment, physical disability, swollen joints, tender joints, acute phase reactants, physician global assessment, radiographs of joints in studies of one or more years' duration)						
Kirwan 2003	COS only	Not specified	Not specified	Rheumatoid arthritis clinical trials	Series of meetings and discussion sessions	Conference participants who had registered for the workshop including patients	Europe, North America
Outcomes	8 (pain, patient global assessment, physical disability, swollen joints, tender joints, acute phase reactants, physician global assessment, radiographs of joints in studies of one or more years' duration) plus recommendations to explore inclusion of subjective experiences of rheumatoid arthritis identified by patients, e.g. sense of wellbeing, fatigue, disturbed sleep						
Kirwan 2005	COS only	Not specified	Not specified	Rheumatoid arthritis clinical trials	Overview presentations, discussion groups and plenary sessions	Participants at the Patient Perspective Workshop at OMERACT 7 including 19 patients	Europe, Australia
Outcomes	8 (pain, patient global assessment, physical disability, swollen joints, tender joints, acute phase reactants, physician global assessment, radiographs of joints in studies of one or more years' duration) plus recommendation that fatigue be included						
Kirwan 2007	COS only	Not specified	Not specified	Rheumatoid arthritis clinical trials	Discussion groups in workshop	Participants at the Patient Perspective Workshop at OMERACT 8 including 20 patients from 10 countries and 60 other OMERACT participants	Europe, North America
Outcomes	8 (pain, patient global assessment, physical disability, swollen joints, tender joints, acute phase reactants, physician global assessment, radiographs of joints in studies of one or more years' duration) plus recommendation that fatigue be included						
Eczema							
Schmitt 2007	Outcomes only	Not specified	Therapeutic interventions for atopic eczema	Randomized controlled trials and clinical practice	Systematic review and survey of clinical experts and patients	Dermatology experts, patients, carers	Europe

Outcome recommendations	Only SCORAD, EASI and POEM perform adequately and should be used in future studies						
Sepsis and critical care							
Marshall 2005	COS only	Not specified	Not specified	Sepsis clinical trials	Expert colloquium	Sepsis researchers, clinical epidemiologists, experts in the development and implementation of outcome measures in rheumatology, neurology and oncology	North America, Europe, Australia, Asia
Outcomes	2 (mortality beyond 28 days, health-related quality of life)						
Goldstein 2005	Wider trial design issues	Age 0-18 years	Not specified	Clinical trials in pediatric sepsis	Consensus conference	20 experts in sepsis and clinical research	North America, Europe
Outcomes	2 (mortality, overall level of functioning)						
Female sexual dysfunction							
Basson 2000	Wider trial design issues	Female	Not specified	Not specified	Delphi, Consensus conference	19 experts in female sexual dysfunction	North America, Europe
Outcomes	3 (specific changes in sexual function, personal distress, quality of life						

Appendix 6: Matrix for assessing NIHR HTA applications (Chapter 4)

Funder ID	COMET database searched	Search for COS from other source	COS included in the study	If no search for COMET/COS (or no COS found) source accessed to inform outcome choice					
				PPI opinion	Outcomes used in other trials	Recommended by a professional body	Feedback from the funding board	Information from a pilot trial	Practitioner opinion
xxx/xxx	Y	N	Y						
xxx/xxx	Y	N	N	The patients have already approved our principal outcome measures					
xxx/xxx	N	Y	Y						
xxx/xxx	N	Y	N	The outcomes have been selected for being well developed, standardised measures with good . . . properties and which assess outcomes identified as important by patients.	Our decisions about which measures to use were informed by previous trials	Our decisions about which measures to use were informed by previous trials, . . ., and the . . . funded review of . . . outcome measures		We have also taken into account our own . . . feasibility study.	
xxx/xxx	N	N	N	Our primary endpoint is a clinical outcome (important and relevant to the patient and the . . .)			The primary outcome has been reviewed, reconsidered and refined to address the Board's concerns.		

Appendix 7: NIHR HTA survey questions (Chapter 4)

*mandatory fields

COS 1: Survey for applicants who had mentioned the COMET website or COS and had found and used a COS that had been published or was in development.

1. What is your name please?
2. Please enter your project title or NETSCCID*

HTA guidance notes for applicants

3. When completing your HTA application did you refer to the guidance notes for applicants?*
   No – (to question 4)
   Yes – (to question 5)

4. If you did not refer to the guidance notes please select any of the following that apply*
   - I have applied to the HTA funding scheme previously and was already aware of the application procedure
   - I was not aware of the guidance notes for applicants
   - Other – please specify

Selection of outcomes for your HTA applications
In January 2012, the NIHR HTA added the following statement to its guidance for applicants: "Details should include justification of the use of outcome measures where a legitimate choice exists between alternatives.

- Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established."

We understand that you may have included a core outcome set (COS) in your application, or used a COS in development to inform your choice of outcomes

5. How did you find out about the COS that you included in your application?*
   Search of the COMET Initiative website
   Search of the literature
   Involved in the development of the COS
   Other – please specify

6. What influenced your decision to use the COS?

7. Did you critically appraise the approach to COS development?
   Yes – please got to question 8
   No - please go to question 9

8. If yes, what factors did you consider?

9. Is there anything else that you would like to tell us about choosing outcomes for your study?

10. If you agree to be contacted about further studies relating to this PhD project please provide your email address:
    Email:

COS 2: Survey for applicants who had mentioned the COMET website or COS and had not found a relevant COS for their trial.

1. What is your name please?
2. Please enter your project title or NETSCCID*

HTA guidance notes for applicants

3. When completing your HTA application did you refer to the guidance notes for applicants?*
   No – (to question 4)
   Yes – (to question 5)

4. If you did not refer to the guidance notes please select any of the following that apply*
   - I have applied to the HTA funding scheme previously and was already aware of the application procedure
   - I was not aware of the guidance notes for applicants
   - Other – please specify

Selection of outcomes for your HTA applications
In January 2012, the NIHR HTA added the following statement to its guidance for applicants: "Details should include justification of the use of outcome measures where a legitimate choice exists between alternatives.
   - Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established."

We understand that you may have searched for a core outcome set (COS) but did not find one that was relevant to your study.

5. Which of the following did you do to find out if a COS existed that was relevant to your study? Select all that apply*
   Search of the COMET Initiative website
   Search of the literature
   Did not search for a COS
   Other – please specify

6. Did you find a COS that may have been relevant to the health condition in your study even if it was not an exact fit for your trial?*
   Yes – go to question 7
   No – go to question 9

7. Did you use the COS to inform your choice of outcomes?*

Yes
No

8. Please give details*

9. Did any of the following influence your choice of outcomes?*
   Patient and public involvement
   Outcomes had been used in other trials
   Informed by a feasibility trial
   Feedback from the funding board
   Other, please specify

10. Please explain how each of your answers above influenced your choice*

11. Is there anything else that you would like to tell us about choosing outcomes for your study?

12. If you agree to be contacted about further studies relating to this PhD project please provide your email address:
    Email:

COS 3: Survey for applicants who had not mentioned the COMET website or COS but had given reasons for their choice of outcomes.

1. What is your name please?
2. Please enter your project title or NETSCCID*

HTA guidance notes for applicants

3. When completing your HTA application did you refer to the guidance notes for applicants?*
   No – (to question 4)
   Yes – (to question 5)

4. If you did not refer to the guidance notes please select any of the following that apply*
   - I have applied to the HTA funding scheme previously and was already aware of the application procedure
   - I was not aware of the guidance notes for applicants
   - Other – please specify

Selection of outcomes for your HTA applications
In January 2012, the NIHR HTA added the following statement to its guidance for applicants: "Details should include justification of the use of outcome measures where a legitimate choice exists between alternatives.

- Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established."

5. Did you do any of the following to find out if a Core Outcome Set (COS) existed that was relevant to your study? Select all that apply.*
   Search of the COMET Initiative website
   Search of the literature
   Did not search for a COS
   Other – please specify

6. Did you find a COS that may have been relevant to the health condition in your study even if it was not an exact fit for your trial?*
   Yes – go to question 7
   No – go to question 9

7. Did you use the COS to inform your choice of outcomes?*
   Yes
   No

8. Please give details*

9. Is there anything else that you would like to tell us about choosing outcomes for your study?

10. If you agree to be contacted about further studies relating to this PhD project please provide your email address:
    Email:

COS 4: Survey for applicants who had not mentioned the COMET website or COS and did not give reasons for their choice of outcomes.

1. What is your name please?
2. Please enter your project title or NETSCCID*

HTA guidance notes for applicants

3. When completing your HTA application did you refer to the guidance notes for applicants?*
   No – (to question 4)
   Yes – (to question 5)

4. If you did not refer to the guidance notes please select any of the following that apply*
   - I have applied to the HTA funding scheme previously and was already aware of the application procedure
   - I was not aware of the guidance notes for applicants
   - Other – please specify

Selection of outcomes for your HTA applications
In January 2012, the NIHR HTA added the following statement to its guidance for applicants: "Details should include justification of the use of outcome measures where a legitimate choice exists between alternatives.

- Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET

Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established."

5. Did you do any of the following to find out if a Core Outcome Set (COS) existed that was relevant to your study? Select all that apply.*
   Search of the COMET Initiative website
   Search of the literature
   Did not search for a COS
   Other – please specify

6. Did you find a COS that may have been relevant to the health condition in your study even if it was not an exact fit for your trial?*
   Yes – go to question 7
   No – go to question 9

7. Did you use the COS to inform your choice of outcomes?*
   Yes
   No

8. Please give details*

9. Did any of the following influence your choice of outcomes?*
   Patient and public involvement
   Outcomes had been used in other trials
   Informed by a feasibility trial
   Feedback from the funding board
   Other, please specify

10. Please explain how each of your answers above influenced your choice*

11. Is there anything else that you would like to tell us about choosing outcomes for your study?

12. If you agree to be contacted about further studies relating to this PhD project please provide your email address:
    Email:

Appendix 8: NIHR HTA survey email invitation (Chapter 4)

Dear Sir or Madam

I am a PhD student at the University of Liverpool supervised by Professor Paula Williamson, Dr Jamie Kirkham, Professor Bridget Young (University of Liverpool) and Professor Mike Clarke (Queen's University Belfast).

My PhD project aims to identify methods to assess and improve the uptake of core outcome sets by clinical trialists. The COMET Initiative (http://www.comet-initiative.org/) defines a core outcome set as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care.

We have recently completed a review of researcher-led NIHR HTA applications submitted between January 2012 and December 2015 to find information about how trialists choose the outcomes to include in their studies. We would like to follow up this review with a short survey, which should only take 10 minutes to complete, to find out more about the use of core outcome sets and how outcomes are chosen for clinical trials.

As an applicant to the researcher-led NIHR HTA programme between January 2012 and December 2015 we would like to invite you to complete the short survey.

Approval for this survey has been received from the NIHR HTA and The University of Liverpool Research Ethics Committee. Completion of the survey will be taken as your consent to participate in this study. All information will be kept strictly confidential. Any information, including quotes, published from the survey will be fully anonymised and not lead to the identification of individual studies or applicants. After the study has been finished, the results will be written up as part of Karen Barnes's PhD thesis, published in academic journals and presented at conferences. If you wish, you will be provided with a copy of the final research report.

To complete the survey please click on the link. We would be grateful if you would complete the survey by **Friday 8th September 2017**.

If you agree to be contacted about further studies relating to this PhD project please provide your email address at the end of the survey.

If you have any queries or would like more information about this study please contact Karen Barnes Karen.Barnes@liverpool.ac.uk

Kind regards
Karen Barnes

Appendix 9: Interview topic guide (Chapter 5)

Interview topic guide

Outcomes

Selecting outcomes for the trial

- Walk me through how you and the team decided on which outcomes to measure in [trial name]
- Which members of the trial team were involved in choosing the outcomes for the trial?
- What or who influenced your choice of outcomes?
  Prompt - What sources of information informed your decisions? Who did you ask?

Awareness of problems with outcomes

- Tell me about any problems you see with the outcomes that are measured in trials in your clinical area?
  Prompt – are there differences in the outcomes measured across trials in your clinical area? Are the outcomes relevant to patients and healthcare professionals (HCP)?
- What is the impact of these problems?
- When you were deciding on outcomes for [trial name] did you consider the possibility of the findings eventually being combined with those from other trials. Did you take any steps to make sure that your results could be combined? Can you describe what steps you took?
- How did you make sure that your chosen outcomes were relevant to HCP and patients?

Core outcome sets

Before the interview I sent you a paper about a core outcome set that is linked to your clinical area.

Knowledge/awareness of COS

- Were you aware of COS before you read the paper? If yes, how did you find out about COS?
- [If interviewee didn't know about COS, or that particular COS], how would you choose to be notified about the COS? Who should notify you/disseminate the COS?
- Can you tell me about what you see as the reasons for developing COS? What are the overall goals?
- Are the goals achievable?
- What are the drawbacks of using COS?

Confidence in COS

- What did you think of the methods used to develop the COS in the paper I sent to you?
- Who should be involved in the development process?
- In what ways would the methods used and stakeholders involved in developing a COS influence your decision to use it?
- What part should trialists play in the development of COS?
  Prompt - At what point should they be involved? Would you get involved in COS development?
- What key things should developers consider when deciding on which outcomes will be included in the COS?
  Prompt – HCP/patient burden and current available measures

- Was it clear from the COS publication which outcomes are in the COS? How did the outcomes in the COS compare to the outcomes you chose? Do you agree with the COS?
- Is there any more information that you would like see provided to enable you to use the COS?

Using COS

- Did you use a COS in your trial? What influenced your decision to use or not use a COS?
- If you weren't aware of COS before, would you use one now? What would influence your decision?
- If more than one COS exists for your area how would you decide which to use? What information would you need to judge which was most suitable?
- If a funder recommended that applicants use a COS, would it influence your decision to use COS?
  Or a clinical trials registry?
  Or a journal?
- Would it be helpful to be reminded about COS when designing your trial? Who should do that? e.g. funder
- What other things would motivate you to use a COS?

Closing interview

- That's the end of my questions. Is there anything else that is important to you that we haven't talked about?
- Is there anything else you'd like to say?

Close interview

Appendix 10: Interview email invitation (Chapter 5)

Dear [Name of Chief Investigator]

I am a PhD student at the University of Liverpool supervised by Professor Paula Williamson, Professor Bridget Young, Dr Jamie Kirkham (University of Liverpool) and Professor Mike Clarke (Queen's University Belfast).

I'm carrying out a study looking at how outcomes are chosen within clinical trials and exploring clinical trialists' views on the role and implementation of core outcome sets.

As the [Chief Investigator of] [name of trial] I'd like to invite you to take part in a telephone interview about choosing outcomes for your trial and your views on core outcome sets. Hearing about your experience is very important to us and will help us to understand influences on the uptake of core outcome sets.

I've attached a leaflet giving more information about the study and would be very grateful if you would please reply to this email to let me know whether you are willing to be interviewed. I will then be in touch to arrange a convenient time for the interview. Please do contact me by email (Karen.Hughes@liverpool.ac.uk) or telephone (0151 794 9753) if you would like further information about the study or have any queries.

Thank you for taking the time to read this email.

Yours sincerely

Karen Hughes

Appendix 11: Interview study information sheet (Chapter 5)

Researchers' experiences of choosing outcomes for clinical trials

You are being invited to participate in a research study. Before you decide whether to participate please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand.

Who is doing the study?

This study is being carried out by me, Karen Hughes. I'm a PhD student funded by the Medical Research Council Network of Hubs for Trials Methodology Research and based in the Department of Biostatistics, University of Liverpool.

What is the purpose of the study?

I'm part of a team exploring the suitability and implementation of core outcome sets in clinical trials[1]. We're keen to learn from clinical trialists about how outcomes are chosen for clinical trials, the challenges of deciding on outcomes, and what helps or hinders the uptake of core outcome sets.

Why have I been chosen to take part?

We're inviting you to take part because you've experience of deciding which outcomes will be included in a clinical trial.

Do I have to take part?

No. Your participation is voluntary. If you choose to take part you're free to withdraw from the study at any time without giving a reason and you can ask for your data to be destroyed before it is fully anonymised.

What will happen if I take part?

I will ask you to take part in an interview that will last for about an hour. During the interview I'll ask about the process of choosing outcomes for your trial and any challenges that you

[1] The COMET Initiative (http://www.comet-initiative.org/) defines a core outcome set as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care.

encountered. Before the interview I'll send you a paper about a core outcome set that's linked to your clinical area. If possible, it would be great if you could look over the paper before the interview as I'd like to hear your opinion of the core outcome set. If you're not able to read the paper before the interview I'd still like to interview you. With your permission, the interviews will be audio-recorded.

Where will the interview take place?

The interviews will usually be conducted by telephone at a date and time of your choosing.

Are there any risks in taking part?

We do not expect there to be any risks from being interviewed in this study. If there are any questions that you do not wish to answer please let me know and I'll move on to the next question. You can stop the interview at any point and do not need to give a reason.

Are there any benefits in taking part?

You will be helping to inform the development of good practice guidance for implementation and uptake of core outcome sets.

How will my data be used?

The University processes personal data as part of its research and teaching activities in accordance with the lawful basis of 'public task', and in accordance with the University's purpose of advancing education, learning and research for the public benefit.

Under UK data protection legislation, the University acts as the Data Controller for personal data collected as part of the University's research. The Principal Investigator acts as the Data Processor for this study, and any queries relating to the handling of your personal data can be sent to the Principal Investigator Bridget Young (Bridget.Young@liverpool.ac.uk).

Further information on how your data will be used can be found in the table below.

How will my data be collected?	An interview that will be audio recorded
How will my data be stored?	All the information that you provide during the study will be stored in locked filing

	cabinets and/or password protected university computers.
How long will my data be stored for?	Once transcribed audio recordings will be destroyed. All other research data (consent forms, anonymised interview transcripts, field notes, and contact details) will be kept in locked filing cabinets and/or password protected university computers for ten years.
Will my data be anonymised?	Audio recordings will be assigned a number and interview transcripts will have all identifying information removed, e.g. participant's name, places and study name. Clinical areas will be left in transcripts to assist the analysis and interpretation.
Who will have access to my data?	Only Karen Hughes will have access to information about you. Her supervisor, Bridget Young, may listen to a recording of the interview to give advice about interviewing technique. Interviews will be transcribed by a professional transcription service that has an online encrypted file transfer facility and will adhere to a confidentiality agreement. Karen Hughes, Bridget Young and Paula Williamson will have access to the anonymised transcripts.

What will happen to the results of the study?

After the study has finished I will write up the findings as part of my postgraduate research thesis and submit this for examination. I will also disseminate the findings in academic journals and conferences. If you wish, I can send you copies of my final research reports. All identifying details will be removed before the results are written up and quotes will be anonymised.

What if I am unhappy or if there is a problem?

If you are unhappy, or if there is a problem, please contact me, Karen Hughes, on 0151 794 9753 (Karen.Hughes@liverpool.ac.uk), so I can try to help. If you remain unhappy or prefer to speak to someone else then you should contact the University of Liverpool Research Ethics and Integrity Office at ethics@liverpool.ac.uk. When contacting the Research Ethics and Integrity Office, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

The University strives to maintain the highest standards of rigour in the processing of your data. However, if you have any concerns about the way in which the University processes your personal data, it is important that you are aware of your right to lodge a complaint with the Information Commissioner's Office by calling 0303 123 1113.

Who can I contact if I have further questions?

Get in touch with the researcher, Karen Hughes:

Karen Hughes

Department of Biostatistics, Block F Waterhouse Building, Liverpool, L69 3GS

Email: Karen.Hughes@liverpool.ac.uk

Tel: 0151 794 9753

The contact details of the Principal Investigator are:

Bridget Young

Department of Health Services Research, Block B Waterhouse Building, Liverpool, L69 3BX

Email: Bridget.Young@liverpool.ac.uk

Tel: 0151 794 5525

Karen's PhD studentship is supervised by Professor Paula Williamson and Professor Bridget Young (University of Liverpool), Professor Jamie Kirkham (University of Manchester) and Professor Mike Clarke (Queen's University Belfast).