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Complete List of Authors:	Kirkham, Jamie; The University of Liverpool, Biostatistics Clarke, Mike; All-Ireland Hub for Trials Methodology Research, Centre for Public Health Williamson, Paula; University of Liverpool
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An assessment of the uptake of core outcome sets using ClinicalTrials.gov

Jamie J Kirkham, senior lecturer[1*]; Mike Clarke, professor[2]; Paula R Williamson, professor[1]

[1]MRC North West Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool, Liverpool, United Kingdom

[2]Northern Ireland Methodology Hub, Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom

[*]**Corresponding Author:**

Dr Jamie Kirkham

Department of Biostatistics
University of Liverpool
Block F Waterhouse Building,
1-5 Brownlow Street, Liverpool,
L69 3GL

Email: jjk@liv.ac.uk
Tel: +44 (0) 151 794 9731

Abstract

Objective: To assess the uptake of the rheumatoid arthritis core outcome set using data in clinical trial registry entries.

Design and Setting: A review of randomised trials of pharmacological interventions for the treatment of rheumatoid arthritis identified on *ClinicalTrials.gov* as having been registered between 2002 and 2016. Full publications were identified for completed studies from the trial registry information or from a search of Google and a citation database, Web of Science.

Methods: The main outcome measure was the proportion of trials planning to measure the rheumatoid arthritis core outcome set from the information presented in trial registry entries. The result was compared with the proportion reporting the core outcome set in the resulting trial publications.

Results: The review revealed that 67% (184/273) of trialists planned to measure the full rheumatoid arthritis core outcome set. Of the subset of 122 trials where a trial publication was available, 102 (84%) reported the full rheumatoid arthritis core outcome set in the trial publication, compared to an uptake estimate of 76% (93/122) based on an assessment of the trial registry entries alone for those studies.

Conclusions: The use of the rheumatoid arthritis core set of outcomes has continued to rise over time in trials. Using the outcomes listed for the studies in a trial registry is likely to provide a reasonable estimate of the uptake of a core outcome set, and is less time consuming than examining the outcomes in published reports of trials. The methods proposed provide an efficient and up-to-date approach for assessing the uptake of the 300 core outcome sets published.

What is known on this subject?

- Core outcome sets can enhance the relevance of research by ensuring that a standardised set of outcomes are measured and reported in all trials for a specific clinical area.
- Assessing uptake allows the impact of core outcome set development work to be evaluated, in order to improve implementation and ensure core outcome sets do not themselves contribute to the waste in research by not being used.
- Previous research involving the uptake of core outcome sets have proven to be time-consuming an inefficient.

What this study adds:

- The reporting of the rheumatoid arthritis core set of outcomes in published trials was found to be 84%. This corresponded to an uptake rate of 76% from the outcomes listed in a trial registry.
- Reviewing outcomes listed in trial registries provides a reasonable estimate of the uptake of a core outcome set, and is less time consuming than examining the outcomes in published reports of trials.
- The methods proposed provide an approach for assessing the uptake of the 300 core outcome sets published.

Introduction

The selection of appropriate outcome measures is crucial to the design of randomised trials. If a trial's findings are to influence health care, the outcomes that are measured and reported need to be relevant to patients, healthcare professionals and others making decisions regarding healthcare provision.

Core outcome sets (COS) can enhance the relevance of research by ensuring outcomes of importance to health service users and other people making choices about health care in a particular setting are measured routinely [1]. The OMERACT (Outcome Measures in Rheumatology) Initiative advocates the use of COS and strives to improve outcome measures in musculoskeletal conditions through data driven multi-stakeholder consensus processes [2].

Following the first OMERACT conference in 1992, the World Health Organization (WHO) and International League of Associations for Rheumatology (ILAR) ratified a COS for clinical trials of symptom-modifying anti-rheumatic drugs in rheumatoid arthritis. The WHO-ILAR rheumatoid arthritis COS (from here forward referred to as the RA COS) was published in 1994 and consisted of seven measures (tender joints, swollen joints, pain, physician global assessment, patient global assessment, physical disability and acute phase reactants), and one additional outcome (radiographs of the joints) for studies lasting one or more years [3].

Assessing the uptake of COS allows the impact of COS development research to be assessed. The uptake of the RA COS has been previously assessed using a sample of 204 randomised trials of pharmacological treatments identified from those included in 31 Cochrane Reviews of interventions for rheumatoid arthritis [4]. There was an increase in the proportion of trials reporting the COS items over time, with almost 70% measuring all these outcomes in trials that were published at the end of the first decade of the twenty first century. However, assessing the uptake of a COS in this way can be a lengthy process because each individual trial report needs to be found and examined. Moreover, many systematic reviews can be several years old, meaning that the most up-to-date trials may not be included in the assessment.

In this research article, we investigate the use of trial registries as a more efficient approach and up-to-date resource for assessing COS, again using the RA COS as our target example. We also compare the uptake rates obtained by examining the trial registry entries with those obtained by checking the published reports of completed studies from within the registry, and see if there has been any improvement in the uptake of the RA COS since our previous study.

Methods

Assessment of trial registry entries

We searched the trials registry *ClinicalTrials.gov* to identify all phase III/IV pharmacological clinical trials of rheumatoid arthritis that had been registered on the site. To identify potentially relevant trials we applied the following filters; 'Conditions: Rheumatoid Arthritis', 'Study Type: Interventional Studies' and 'Phase: 3 and 4'. The returned hits were then screened by a single reviewer (JJK). Trial registry entries were excluded if the trial was not exclusive to rheumatoid arthritis participants (e.g. also contained osteoarthritis participants), did not consider efficacy as an endpoint (e.g. were safety, pharmacokinetic (PK)/pharmacodynamic (PD)/immunology studies only), considered a non-pharmacological intervention or device, were non-randomised studies, were diagnostic test accuracy studies or were studies where all participants received the same intervention (single group assignment). We applied these exclusions because these types of studies were beyond the scope of the current RA COS.

For each eligible trial registry entry, information was extracted on all planned trial outcomes and an assessment was made as to whether the full RA COS set was listed. If trialists had registered a composite outcome measure, for example the American College of Rheumatology (ACR) improvement criteria [5], all the individual outcomes in the composite were considered in the assessment, even if they were not listed separately. For example, if the ACR 20 criteria were specified and the trial was less than 52 week in duration, then we assumed the full RA COS was assessed. The assessments were carried out by one reviewer (JJK), who has previous experience with the assessment of the uptake of the RA COS with the support of two rheumatologists in the previous research [4].

Assessment of trial reports

We searched for trial publications for all eligible trials that had been identified on the trial registry. Publications were either registered on the trial registry site or were identified via a Google search of the clinical trial registry (CTR) number (limited to the first three pages of Google hits) or a search of the CTR number on a citation database, Web of Science. Publications that were linked to the trial CTR number, but

did not report on the trial findings were excluded. An assessment of whether the full RA COS was reported in each trial publication was carried out in the same way as for the trial registry entries.

Assessment of the uptake of the RA-COS

Two measures of uptake were of interest; the proportion of trials that planned to measure the full RA COS (based on the outcomes listed in the trial registry), and the proportion of trials that reported the full RA COS (based on published reports of completed trials that had been identified via the trial registry). To assess how the measurement of core outcomes had changed over time, the data from the trial publications from the previous assessment (systematic review approach) [4] was combined with the data from the trial publications from this new assessment (trial registry entry approach). Any publications that were identified by both approaches was removed, so that each publication contributed once only to the analyses. We ordered the published trials by publications date, divided them into blocks of ten and calculated a moving average of the proportion reporting the full RA COS. In calculating the moving average, the percentages from the later trials included in the original assessment was amended slightly to take into account of the addition of new trials in this updated assessment.

Ethical approval: Not required.

Patient involvement: No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results

Assessment of trial registry entries

After applying the relevant filters, a total of 652 rheumatoid arthritis trials were identified on *ClinicalTrials.gov*, with registration dates from May 8th 2002 to August 17th 2016. Screening identified 366 of these records as ineligible: 138 trials were not exclusive to rheumatoid arthritis, 35 did not consider efficacy as an endpoint, 17 did not consider a pharmacological intervention and 176 did not use an eligible study design for this assessment (Figure 1). Following a review of the outcome specifications within the registry entry, a further 13 records were excluded: 12 due to poor outcome specification (e.g. remission was specified as an outcome, but the criteria for remission was not defined) and one entry did not specify any outcomes (entry registered in 2002). This left 273 registry entries for this assessment (Figure 1).

Of the 273 eligible registry entries, the recruitment status of 167 (61%) was shown as completed in *ClinicalTrials.gov* while for the remaining 106 entries, recruitment was either ongoing, not started or the study was either on hold or terminated prematurely (Table 1). Similar proportion of trials planned to follow their participants for less than six months and for at least twelve months. The majority of trials received commercial funding (Table 1). About half the trials had a planned recruitment of between 100-500 participants (49%; 134/27), and just over a third planned for more than 500 participants (35%; 96/273). We found a trial publication for nearly half the registered trials (45%; 122/273). Publications were listed on *ClinicalTrials.gov* for 97 trials, and we found the remainder from our searches of Google and Web of Science. The median time from the trial start date (date that enrollment to the protocol began) recorded on the trial registry to the first recorded publication date (as recorded on the journal article) was about five years (Table 1). Of the 151 trials that had no trial publication, trial data were available on *Clinicaltrials.gov* for 21. In the remaining 130 trials where no trial publication could be found, 67 were ongoing studies (with this coding shown as verified by the study authors in the last two years) and no information on whether the trial was completed or where the data could be found was available for 63 trials (Table 1).

Uptake of the full RA COS

A review of the outcomes specified in the 273 trial registry entries overall revealed that 67% (184/273) planned to measure the full RA COS. Of the subset of 122 trials where a trial publication was available, 102 (84%) reported the full RA COS in the trial publication, compared to an uptake estimate of 76% (93/122) based on an assessment of the trial registry entries alone for those studies (Table 2).

The uptake rate remains at 76% (109/143) if the 21 trials where data are available on the trial registry are considered to be published, despite there being no trial publication. Sixteen of these additional 21 trials reported data on the full RA COS in the trial registry. 17 published studies did not list the full RA COS in either the trial registry entry or the trial report. A full list of similarities and discrepancies between the outcomes mentioned in the two source documents in relation to the RA COS are presented in Table 2.

Uptake of the RA-COS over time

The reporting of the full RA COS in the trial publication over time is illustrated both for the previous approach of identifying trial publications from the inclusion of studies in systematic reviews (reported in [4]) and the new approach of identifying trial publications from trial registry entries (Figure 2). Thirteen trials appeared in both evaluations but were used only once in the following analyses. In the period 2006 to 2009, we found ten new trials that were published in the overlap period which were not included in our original evaluation. Figure 2 shows a clear continuation in the upward trend in the proportion of trials measuring the full RA COS, with nearly 85% measuring all the core outcomes in trials that were published in 2016.

Discussion

This study has demonstrated that the uptake of the RA COS which was published in 1994 has continued to rise over time, with nearly 85% of trials published in 2016 measuring the full RA COS (Figure 2). The increase in uptake was encouraging but the plateau in recent years perhaps suggests that further advances may be challenging, especially as some trialists do not measure the full RA COS even though they are aware of its existence [4]. In the previous assessment of the RA COS [4], we noted that the introduction of regulatory guidance, e.g. from the Food and Drug Administration (FDA) (1996) [6] and European Medicines Agency (EMA) (1998) [7], which were involved in ratifying and recommending the RA COS, may have contributed to trials measuring these core outcomes. Over 80% of the trials in this assessment received some commercial funding and, therefore, their adherence to the EMA/FDA guidance may have resulted in trialists using the RA COS. This suggests that implementation plans to help increase the uptake of the COS in the future might include an emphasis on guidance encouraging good practice in the design, implementation and reporting of clinical trials.

A review of the outcomes listed on the trial registry suggested that the uptake of the RA COS across all trials registered would be 67%. Considering only those trial registry entries for which a publication was found, the uptake rate based on trial registry entry data alone (not reading publications) was 76%; this compared favourably to the uptake rate of 84% based on an assessment of the associated trial publications. Discrepancies in reported outcomes (in a trial report) that are not pre-specified (in a trial registry) have previously been found to be high [8]. Despite this difference in the number of trial registry entries listing the full RA COS and the number of trial publications doing so, we found that the use of trial registry entries to assess COS uptake was efficient and provides a more up-to-date method than identifying trials because of their inclusion in systematic reviews. It is also preferable to citation analysis, which is the only other method we have identified as having been used to assess the uptake of a COS [9]. That approach has also been applied to the RA COS, but proved unreliable because few trial authors cited the COS publication, despite measuring the COS [9].

The strength of our study is that we considered all rheumatoid arthritis trials registered on *ClinicalTrials.gov*, which is one of the largest clinical study registries in the world. While we acknowledge that more trials could have been identified if more primary registries were searched, such as all those registered with the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), there is no reason to believe that the trials identified on *ClinicalTrials.gov* are not a representative sample of all trials in rheumatoid arthritis, given that trials entered onto the site are registered from across the world [10]. Furthermore, since the International Committee of Medical Journal Editors (ICMJE) accepts registration in any registry that is a primary register of ICTRP or in *ClinicalTrials.gov* (a data provider for ICTRP), we do not anticipate that the trials registered in *ClinicalTrials.gov* will differ in quality given that all trial registries endorsed by ICMJE must meet the same criteria [11]. One potential difference between a sample drawn from *ClinicalTrials.gov* and from other registries is that the percentage of commercially funded trials on this US-based registry might be higher, which might lead to higher estimates of COS uptake if such trials are more likely to use the COS for regulatory reasons. From a practical sense for considering ways to assess COS uptake, we found that *ClinicalTrials.gov* had a user friendly interface, which helped make this an efficient source of the outcomes measured in studies when assessing COS uptake. With this in mind, similar assessments should be carried out for COS from other therapeutic areas and the work presented here provides a template for an efficient method to conduct such assessments.

A potential limitation of this study is that the assessments were carried out by one reviewer (JJK), but the instruments used to measure the core outcomes in rheumatoid arthritis trials were previously defined with the help of two rheumatologists in a previous RA COS assessment [4]. When considering the outcomes reported in trial publications, we also relied heavily on trial authors registering their publications on *Clinicaltrials.gov*. Although we supplemented this with internet searches using Google and a single citation database, we are likely to have missed some trial reports. However, the identification of the outcomes that are actually measured in trials (as included in reports or datasets) as compared to those that are planned to be measured (as included in registry entries) should become easier in the future, for example due to US legislation (effective on *Clinicaltrial.gov* from January 2017), mandating the uploading of summary trial results within a certain time frame, independent of decisions made about journal publication [12].

In the broader context, a recently updated systematic review has identified around 300 published COS and nearly 150 ongoing COS [13] and this report provides evidence to support the potential value of these to improving the quality of research and reducing waste. This report highlights the successful implementation of a well-established COS in rheumatoid arthritis. Although it appears to taken over 20 years to reach an uptake rate of nearly 85% for this COS, the promotion of COS by the COMET (Core Outcome Measures in Effectiveness Trials) [14] Initiative, and its referencing in guidelines for trialists [15], funders [16] and regulatory guidance [17], should accelerate uptake in the future. Furthermore, greater awareness of the need to consider the use of a COS and inclusion of links to the COS in registry entries [18] should also have a positive impact, bearing in mind that more than 90% of the queries received by trial registry providers relate to the outcomes section (personal communication Allison Cuff, BioMed Central).

Conclusions

The adoption of a COS has the potential to increase consistency in outcomes measured across trials and ensure that trials are more likely to measure appropriate outcomes. The WHO-ILAR COS (RA COS) for rheumatoid arthritis was first ratified in 1994 and, by the 2010s, nearly 85% of published trials in rheumatoid arthritis are measuring it. This is the first study that has assessed the measurement of a COS using trial registry entries, finding that this was a more efficient and up-to-date approach than retrieving and assessing trial publications, and more reliable than citation analysis. The uptake rate estimated from trial registry data alone (i.e. not requiring a trial publication to be read) appears to be more reliable when based on those trials that did subsequently complete and were published. The recommended method for assessing uptake would therefore be to firstly identify the trials in the registry, select those that have been published (using the linked publications section within the registry) and then use the registry entry (rather than the publication) to check for COS uptake.

Figure 1: Flow diagram of rheumatoid arthritis trials registered on *ClinicalTrials.gov* and included in this study.

Figure 2: Percentage of trials measuring the full rheumatoid arthritis core outcome set (10-point moving yearly average).

Table 1: Trial characteristics and publication status of included rheumatoid arthritis trials registered on *ClinicalTrials.gov*

Table 2: Similarities and discrepancies between the RA COS listed in both the trial registry entry and the trial publication

Contributors

PRW and JJK jointly conceived the idea for the study and are the guarantors for the project. The study methods were designed by JJK, MC and PRW. Identification of the relevant studies and the assessment of the uptake of the core outcomes from each study were carried out by JJK. The analysis was done by JJK and PRW. JJK prepared the initial manuscript. All authors were involved in the revision of this manuscript. All authors read and approved the final manuscript and are accountable for all aspects of the work, including the accuracy and integrity.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; MC and PRW are members of the COMET Management Group; however, the authors have no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

The data from this study are available from the corresponding author (jjk@liv.ac.uk). For each trial identified in the trial registry, information on the planned core outcomes to be measured is available alongside the reported core outcomes from any resultant trial publication.

Transparency

The manuscript's guarantor (JJK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Trial characteristics and publication status of included rheumatoid arthritis trials registered on *ClinicalTrials.gov*

Trial Characteristic	N=273 (%)
Recruitment status[a]:	
Completed	167 (61)
Terminated	18 (7)
Recruiting	46 (17)
Enrolling by invitation	1 (<1)
Suspended	4 (2)
Not yet recruiting	36 (13)
Withdrawn	1 (<1)
Trial duration:	
< 6 months	120 (44)
6-12 months	43 (16)
≥12 months	108 (40)
Not specified	2 (<1)
Funding:	
Commercial	208 (76)
Non-commercial	51 (19)
Both	14 (5)
Planned sample size	
<100	43 (16)
100-500	134 (49)
>500	96 (35)
Primary trial publication status*	
Trial published	122 (45)
Publication listed on ClinicalTrials.gov	*97*
Search for Clinical Trial Registry Number using Google/Web of Science[b]	*25*
No trial publication found but trial data published on *ClinicalTrials.gov*	21 (8)
Recruitment completed (results posted on ClinicalTrials.gov)	*14*
Study was terminated (results posted on ClinicalTrials.gov)	*7*
No trial publication found (no trial data found)	130 (48)
Study is ongoing (verified by authors in last 2 years)	*67*
Unknown study status (trial status not verified by authors in last 2 years)	*12*
Recruitment completed (no results available)	*37*
Study was withdrawn/terminated/suspended (no results available)	*14*
Time to publication (N=122)[c]	
Median:	4 years, 354 days
Interquartile range (1st quartile):	3 years, 263 days
Interquartile range (3rd quartile):	5 years, 142 days

[a] Recorded on *ClinicalTrials.gov* (6th October 2016)
[b] Recruitment status listed as either completed or terminated on *ClinicalTrials.gov*
[c] Taken from start date (date that enrollment to the protocol began, as recorded on *ClinicalTrials.gov*) to first recorded publication date (as recorded in the published article)

Table 2: Similarities and discrepancies between the RA COS listed in both the trial registry entry and the trial publication

Trial Characteristic	N=122
No discrepancies	
All outcomes in RA COS were mentioned in both the trial registry entry and the trial publication	90
All outcomes in RA COS were not mentioned in either the trial registry entry or the trial publication but the outcomes specified in both sources were the same	11
Discrepancies	
All outcomes in RA COS were not mentioned in either the trial registry entry or the trial publication and the outcomes specified in both sources were different	6
All outcomes in RA COS were mentioned in the trial registry entry but not the trial report	3
All outcomes in RA COS were mentioned in the trial report but not the trial registry entry	12