Industry funding was associated with increased use of core outcome sets

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**ABSTRACT**

**Objectives**

The objective of this study was to assess the uptake of the rheumatoid arthritis core outcome set (RA-COS) using data from multiple data providers, and to investigate factors that may influence this uptake.

**Study Design and Setting**

An observational review was carried out on all clinical trials of rheumatoid arthritis that were indexed on the World Health Organisation-International Clinical Trials Registry Platform (WHO-ICTRP). Various measures of COS uptake were calculated from information presented in the trial registries and trial publications. Logistic regression was conducted to investigate factors thought to be associated with planned COS uptake.

**Results**

A total of 341 trials were eligible for the evaluation of RA-COS uptake. In the decade leading up to 2019, the assessment of uptake based on published results was maintained at just over 80%. Trials that were not commercially funded were much less likely to plan to measure the RA-COS than those with industry funding (60% versus 80%; adjusted OR 0.18, 95% CI 0.11 to 0.32; p<0.001).

**Conclusion**

This study has demonstrated that the use of the WHO-ICTRP can identify a large and geographically diverse range of trials to include in the evaluation of COS uptake.

**Keywords:** Clinical Trial Registry;Core Outcome Set; Rheumatoid Arthritis; Uptake; World Health Organisation International Clinical Trials Registry Platform

**What is new?**

* This review is an update of the uptake of the RA-COS using information from multiple data providers registered with the WHO-ICTRP as opposed to the single data provider ClinicalTrials.gov.
* In the decade leading up to 2019, the assessment of RA-COS uptake based on published results was maintained at just over 80% (Figure 2).
* It was found that trials that were not commercially funded were much less likely to plan to measure the RA-COS than those with industry funding (Table 2). There is a need to raise awareness amongst trial funders on COS endorsement in the publically funded sector.
* Use of the WHO-ICTRP to identify trials to include in the evaluation of COS uptake has demonstrated that a larger and more geographically diverse range of trials can be obtained than using ClincialTrials.gov alone, although in this rheumatoid arthritis application, differences in uptake rates were small.
* Those wishing to assess COS uptake need to make a judgment as to whether a reasonable estimate of uptake can be obtained by a single data provider or whether multiple providers need to be used. This decision may be influenced by the number of trials available in the condition of interest.

**INTRODUCTION**

Core outcome sets (COS) are useful for increasing relevance, reducing outcome reporting bias and helping with the pooling of results across different research studies [1,2]. Several hundred COS studies have been systematically identified and published to date, with at least two hundred more that are known to be ongoing across a wide variety of clinical areas [3]. Over fifty such COS studies are available for a variety of musculoskeletal diseases, examples include rheumatoid arthritis [4], osteoarthritis [5] and ankylosing spondylitis [6].

A better uptake of COS would help towards the aim of improving health by ensuring important outcomes relevant to those making choices about healthcare are routinely measured. In rheumatoid arthritis, two assessments of COS uptake have already been undertaken. Those studies demonstrated that over 80% of trials that involved a pharmacological treatment for rheumatoid arthritis were measuring the full rheumatoid arthritis COS (RA-COS) by the year 2016 [7-8]. The more recent study used a rapid review approach to assess uptake by utilising both planned and reported outcomes listed on the clinical trials registry, ClinicalTrials.gov [8]. However, a potential limitation of the study was that about 40% of studies registered on ClinicalTrials.gov have the USA as the location of trial registration [9]. This may be particularly influential on COS uptake for this condition, given that prior to the ratification of the RA-COS, it was noted that clinical trials involving patients with rheumatoid arthritis in the USA measured different outcomes to those conducted in Europe [10].

In this new study, the objective is to evaluate the uptake of the RA-COS using trials registered on the World Health Organisation-International Clinical Trials Registry Platform (WHO-ICTRP), a search portal that includes 17 different data providers from around the world, of which ClinicalTrials.gov is one. Our aim is to determine if there is a difference in uptake of the RA-COS in trials indexed on WHO-ICTRP compared to ClincialTrials.gov alone, as well as providing the most recent uptake statistics for the RA-COS, and exploring factors that may influence COS uptake.

**METHODS**

The methods for assessment of RA-COS uptake closely followed a previous similar study conducted to assess the uptake of the RA-COS using ClinicalTrials.gov alone as the source for trial identification [8]. The RA-COS consists of eight outcomes; tender joints, swollen joints, pain, physician global assessment, patient global assessment, physical disability, acute phase reactants, and in trials lasting at least one year, an assessment of radiological damage [4].

**Identification and assessment of trial registry entries**

We searched the WHO-ICTRP search portal [11] on 9 November 2018 to identify all trials of treatments for people with rheumatoid arthritis that were within scope of the RA-COS. To assist with the search, we applied the following filter: condition ‘rheumatoid arthritis’ and limited the search to phase III and IV trials. The returned records were exported into a spreadsheet and further filters were applied based on additional study design fields that were downloaded. Records were excluded if the study population was not exclusive to participants with rheumatoid arthritis, the intervention type was non-pharmacological, the study design was observational or non-randomised or the study did not consider efficacy as an endpoint. We applied these exclusions because these types of studies were beyond the scope of the current RA-COS [4]. Records were also excluded if no outcomes were listed as a formal assessment of the uptake of the RA-COS could not be made.

If a record was incomplete, the full record was screened individually and the same exclusion criteria were applied. Where there was a lack of data available, the individual trials registries (e.g. ClinicalTrials.gov or ACTR (Australian Clinical Trials Registry)) were additionally checked. Records were also excluded at this stage if outcomes were poorly defined, for example, “efficacy” was listed as a planned outcome but the criteria for measuring efficacy were not defined. Screening for eligibility of all records was undertaken independently by a senior investigator (JJK) and at least one student investigator (MB, LH, KP), and any discrepancies were resolved via discussion.

**Data Extraction**

For each eligible trial registry entry, all planned trial outcomes were extracted and an assessment was made as to whether the full RA-COS was cited. All components of a composite outcome were considered separately when assessing the planned use of the COS. During data extraction we also checked ‘other study IDs’ to determine whether trials were dually registered across multiple trial registries. If a trial was registered more than once it was included only once in the assessment, and it was assumed that the trialists planned to measure the full COS if all outcomes in the COS were listed in one of the entries. To prevent duplication of effort, trials identified on ClinicalTrials.gov that had been assessed (as identified by the unique clinical trial registry number) in the previous assessment of uptake [8] were included in the evaluation of uptake but not re-assessed a second time.

**Identification and assessment of trial results**

Trial results for completed studies were identified from two sources: the results section of the trial registry entry and from trial publications. An assessment of whether the full RA-COS was reported in either of these two sources was carried out in the same way as for the trial registry entries. Assessment was first undertaken based on the trial publication if available, and second using the results in the trial registry if the results had been posted there. If a trial publication was available, results posted on the trial registry were not considered. Relevant publications were found either directly from their listing in the trial registry entry or via a Google search for the clinical trial registry (CTR) number, trial acronym or principal investigator (limited to the first three pages of Google hits). A final search for results and publications was done on 28 March 2019.

**Assessment of uptake**

As with the previous assessment of COS uptake, several measures of uptake were calculated in order to assess the reliability of results when considering data from both trial registries which includes ongoing trials, trial publications from completed trials and a combination of both sources. The uptake measures are listed in Box 1.

|  |  |  |
| --- | --- | --- |
|  | **Numerator** | **Denominator** |
| **Reported Uptake** **(completed studies)** | Number of trials that reported the COS results from any source | Total number of trials where the study results have been made available from any source  |
| **Reported or Planned Uptake (all studies)** | Number of trials that reported the COS in the registry (where a publication or results were identified in the registry) or planned to measure the COS from the outcomes listed on the registry if the publication or results are not available on the registry | Total number of trials included in the assessment (irrespective of results being available) |
| **Planned Uptake (all studies)** | Number of trials that plan to measure the COS based only on data listed in the trial registry  | Total number of trials included in the assessment (irrespective of results being available)  |
| **Reported or Planned Uptake (completed studies)** | Number of trials that reported the COS in the registry (where a publication or results were identified in the registry) or planned to measure the COS from the outcomes listed on the registry if the publication or results are not available on the registry  | Total number of trials that are known to be complete (irrespective of results being available) |

**Box 1: Measures for assessing the uptake of core outcome sets**

When new trial publications were identified, we combined this new data with trial publications from the previous ClinicalTrials.gov assessment [8] in order to provide an update of how the measurement of the RA-COS had changed over time. We ordered the published trials by publication date, divided them into blocks of ten and calculated an average of the percentage reporting the full RA COS over the previous 10 years. For example, the average for year 2019 was taken to be the average percentage of trials reporting on the full RA COS from 2010 to 2019.

**Factors affecting uptake**

A multivariate logistic regression was carried out to investigate whether certain trial characteristics were associated with COS uptake. The binary response variable for each study in the model was the planned uptake using data in the trial registry entry (i.e. the ‘planned uptake (all studies)’ numerator from Box 1), coded as 1 if the study planned to measure the full COS and 0 if they did not. Independent variables included whether the study was prospectively registered, whether the study received partial/complete industry funding, whether the study was registered on ClinicalTrials.gov, whether the results for the study were available and whether the study involved recruiting sites from the USA or low and middle income countries (LMiCs). All independent variables were included in the final model and reflected factors that were routinely reported for all trials with the trial registries and were believed in advance to be potentially influential on uptake in this setting. Economic status for each recruiting site was classified according to the World Bank list of economies, as of June 2018 [12].

**RESULTS**

**Identification of eligible trials from the World Health Organisation search portal**

After searching for phase III/IV trials in rheumatoid arthritis, a total of 892 trials from 13 of the 17 data providers were identified on the WHO-ICTRP search portal from its inception to 9 November 2018. The five data providers with the most trials made up 95% of the studies identified: ClinicalTrials.gov, n=606; EU Clinical Trials Register (EUCTR), n=93; Clinical Trial Registry – India (CTRI), n=58; Japan Primary Registries Network (JPRN), n=53 and Iranian Registry of Clinical Trials (IRCT), n=38.

After applying the additional filters for the study inclusion criteria, 480 of the exported records were ineligible, while a further 42 of the remaining 412 records were excluded following a review of the full trial registry record (Figure 1). Twenty-nine records of the same trial were dually registered and duplicate records were removed such that each trial was only represented once in the assessment. Twenty-seven of these trials appeared in either ClinicalTrials.gov or the European clinical trial registry (EUCTR), with 15 of the duplicates were registered in the Indian registry (CTRI) and 12 in the Japanese registry (JPRN). The remaining two duplicates were separate components of the same trial registered separately in the Iranian registry (IRCT). In total, there were 341 unique records for assessment representing phase III/IV clinical trials of rheumatoid arthritis that considered pharmacological treatments and efficacy as an endpoint.



**Figure 1:**  Flow diagram of rheumatoid arthritis trials registered on the WHO-ICTRP and included in this study

Eighty percent (272/341) of these studies were prospectively registered, 75% (254/341) of studies received at least partial funding support by industry, recruitment was exclusively from a USA site in 7% (23/325) of studies and 4% (15/325) from a low-middle income country (Table 1). 71% (243/341) of eligible studies were primarily registered on ClinicalTrials.gov and 73% (250/341) of studies were completed or terminated (Table 1). Of the completed studies, 79% (197/250) had results, of which 164 were found in journal publications and for 33, the results were available in the trial registry only (Figure 1).

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial Characteristic**  | **N = 341 (%)** | **Trial Characteristic** | **N = 341 (%)** |
| **Primary trial registry as listed on WHO-ICTRP:** |  | **Prospective Registration:** |  |
| Australian New Zealand Clinical Trial Registry | 3 (0.9) | Prospective | 272 (79.8) |
| Brazilian Clinical Trials Registry | 1 (0.3) | Retrospective | 69 (20.2) |
| Chinese Clinical Trial Registry | 3 (0.9) | **Funding:** |  |
| Clinical Trial Registry – India | 15 (4.4) | Commercial  | 254 (74.5) |
| German Clinical Trials Register | 1 (0.3) | Non-commercial | 87 (25.5) |
| EU Clinical Trials Register | 52 (15.3) | **Recruiting countriesa:** |  |
| Iranian Registry of Clinical Trials | 9 (2.6) | Exclusive USA | 23 (7.1) |
| International Standard Randomised Controlled Trials | 1 (0.30) | Exclusive LMiC | 15 (4.6) |
| Japan Primary Registries Network | 13 (3.8) | Not exclusive USA/LMiC | 287 (88.3) |
| ClinicalTrials.gov | 243 (71.3) | **Study status:** |  |
|  |  | Completed/Terminated | 250 (73.3) |
| **Trial duration:** |  | Ongoing | 91 (26.7) |
| Median 26 weeks (IQR 24 weeks to 52 weeks) |  |  |  |

LMiC = Low-Middle income Country

WHO-ICTRP = World Health Organisation-International Clinical Trials Registry Platform

aDenominator = 325

**Table 1:** Trial characteristics of the included rheumatoid arthritis trials registered on the World Health Organisation-International Clinical Trials Registry Platform (WHO-ICTRP)

**Comparison with previous cohort**

Of the 273 included trials in the original ClinicalTrials.gov assessment [8], 262 were identified in our search of the WHO-ICTRP search portal and deemed eligible for inclusion, although 49 of these were registered and linked to another registry on WHO-ICTRP as a primary source of registration (47 EUCTR, 1 ISRCTN, 1 JPRN). Seven of the remaining eleven were identified in the WHO-ICTRP search but on second screening were deemed to be not eligible for this updated study (three were non-efficacy studies, two were non-drug interventions, one was a non-randomised study and one was not exclusive to RA), and only one of these seven planned to measure the full RA-COS. The other four trials while listed on the WHO-ICTRP portal were not identified by the search criteria, and only one of these reported on the full RA-COS. A later investigation revealed that these four were not identified in the search because the trial phase was not provided (n=3) and rheumatoid arthritis was spelt incorrectly (n=1). As a result, 262/273 (96%) of the original trials [8] are also reported in this assessment.

In summary, from the updated search, 79 new unique trials were identified, 30 of the new trials identified were registered on ClinicalTrials.gov, whilst the additional 49 were identified from one of the other trial registries.

**Assessment of the uptake of the rheumatoid arthritis core outcome set**

The four uptake measures listed in Box 1 can be computed using the data presented in the bottom half of Figure 1.

* **Reported Uptake (completed trials):** The percentage reporting data on the full RA-COS was 79% (155/197) for trials identified on the registry as completed when the trial results were found either in the trial registry or published report.
* **Reported or Planned Uptake (all trials):** The percentage reporting or planning to measure data on the RA-COS was 71% (242/341) for trials where results were identified in the registry or where planned measurements were taken from the trial registry entry if results were not available.
* **Planned Uptake (all trials):** The percentage planning to measure data on the RA-COS was 70% (238/341) for registered trials regardless of trial or publication status, based on the outcomes listed in the trial registry entry.
* **Reported or Planned Uptake (completed trials):** The percentage reporting or planning to measure data on the full RA-COS was 75% (187/250) for trials identified on the registry as completed where a publication or results were identified in the registry (i.e., not from a wider search) or where planned measurements were taken from the trial registry entry if a publication or results were not available in the registry.

Planned uptake for all trials listed on ClinicalTrials.gov that were included in the previous assessment was 72% (188/262); this rate did not improve for the thirty new trials identified since 2016 that were registered in the same registry (70%; 21/30). Of the remaining 49 newly identified trials registered since 2005 on one of the other registries, the planned uptake rate was lower (59%; 29/49). In this update, we identified and included an additional 44 new trial publications that we found for the assessment of the RA-COS uptake over time (Figure 2), 29 were new publications from trials included in the previous assessment, and all but one of the remainder were from trials that were not registered on ClinicalTrials.gov. With the additional publications included, the uptake rate remained similar and was maintained at an annual average of just over 80% in the decade up to 2019 (Figure 2). The planned uptake (n=341) and uptake from the reported results (n=197) for each of the eight individual core outcomes is reported in Table S1.



**Figure 2:** Percentage of trials measuring full rheumatoid arthritis core outcome set (RA-COS) averaged over past 10 years. WHO=World Health Organization; ILAR=International League of Associations for Rheumatology. [Note: The Food and Drug Administration (FDA) guideline for the treatment of rheumatoid arthritis was first released in 1996, while the European Medicines Agency (EMA) guideline was based on a version adopted in 1998]

**Factors affecting planned uptake**

Multiple logistic regression analysis showed that trials that were not commercially funded were much less likely to plan to measure the RA-COS than those that received at least partial funding by industry (adjusted OR 0.18, 95% CI 0.11, 0.32, P<0.001) (Table 2). From the study cohort, 80% of industry-funded trials (203/254) planned to measure the RA-COS compared to 60% (52/87) that were not commercially funded. There was no evidence of effect for all other factors considered (Table 2).

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable**  | **Odds Ratioa** | **95% Confidence interval**  | **P-value**  |
| Trial not registered on ClinicalTrials.gov  | 0.77 | 0.38, 1.61 | 0.50 |
| Trial recruiting from sites not exclusive to USA/LMiC (reference)b |  |  |  |
| Trial exclusively recruited from USA | 0.70 | 0.27, 1.84 | 0.47 |
| Trial exclusively recruited from LMiC (all India) | 0.90 | 0.27, 2.95 | 0.86 |
| Trial was retrospectively registered | 0.91 | 0.49, 1.68 | 0.76 |
| Trial was non-commercially funded | 0.18 | 0.11, 0.32 | <0.001 |
| Trial results were available in a publication (reference) |  |  |  |
| No trial results were available | 0.82 | 0.48, 1.42 | 0.48 |
| Trial results were available on trial registry only | 0.81 | 0.32, 2.05 | 0.66 |

LMiC = Low-Middle income Country

a Odds ratios were adjusted for all factors included in the final multivariate regression model

b the complete case analysis contained 325 out of the total 341 eligible records as no recruitment site data was provided for 16 trials

**Table 2: Results of the logistic regression analysis displaying factors that affect planned uptake of the RA-COS**

**DISCUSSION**

The uptake of the RA-COS has been maintained at just over 80% since the previous evaluation [8] was done (Figure 2). There has been relatively little increase in uptake in recent years, which suggests that achieving further improvements in the uptake of the RA-COS might be challenging. Interventions such as the introduction of the RA-COS in regulatory guidance shortly after the publication of the RA-COS in 1994 appeared to have an encouraging effect on the uptake of the COS in subsequent years. The uptake of the individual core outcomes within the RA-COS set (Table S1) revealed that the uptake of radiological damage is lower than the other seven outcomes. Previous research suggests some trialists do not measure damage as is it costly to measure and requires further expenditure to obtain valid readings of radiographs [7]. Such feasibility issues on the measurement of certain outcomes may affect the continual improvement in COS uptake over time. There was a more than 80% decrease in the likelihood of trials planning to measure the RA-COS if the trial was not commercially funded (adjusted OR 0.18, 95% CI 0.11, 0.32, P<0.001). Only 60% of non-commercially funded trials planned to measure the full RA-COS, compared to 80% that received industry funding. There is a need to raise awareness amongst trial funders on COS endorsement in the publically funded sector [13].

We have shown that use of the WHO-ICTRP to identify trials for inclusion in the evaluation of COS uptake allows the identification of a larger and more geographically diverse set of registered trials than searching ClinicalTrials.gov alone. However, the quality of information recorded within some trial registries was variable. As an example, despite an English translation being available, only 3 of the 18 eligible trials from the Chinese Clinical Trials Registry (ChiCTR) were included in the evaluation because the outcome definitions and/or timing of the measurements was poorly/not defined.

All four uptake measures calculated in this current assessment and those using ClinicalTrials.gov alone [8] were similar. As an example, the planned uptake from considering ClinicalTrials.gov (72%) and the full sample (70%) were comparable, although the weighting of these results was strongly in favour of trials registered on ClinicalTrials.gov, given this made up over 85% of the eligible trials. Cochrane guidance recommends that both ClinicalTrials.gov and WHO-ICTRP should be used to search for trials [14], though all trials identified on ClinicalTrials.gov in the previous assessment [8] were also found on WHO-ICTRP, and just four were not picked up in WHO-ICTRP by the basic search strategy because of missing information or errors in the recorded entry.

A recent systematic review of COS showed that far more people from North America and Europe are involved in COS development than in LMiCs [15]. However, although this assessment of COS uptake found only 15 trials that recruited exclusively from a LMiC (all India), there was no evidence of a difference in effect for the planned uptake of the RA-COS between countries recruiting from the USA, LMiC or a mix of sites recruiting from different continents.

### **Strengths and limitations of this study**

The strength of this study is that we used the WHO-ICTRP to identify eligible trials for the assessment of RA-COS uptake. This portal contains data providers from all major continents including Asia, Africa, North America, South America, Europe and Australia and therefore has the potential to include a geographic diverse range of rheumatoid arthritis trials from across the world. The identification, selection and assessment of all eligible trials was also conducted by an experienced researcher (JJK) and at least one student investigator (MB, LH, KP). This was a marked improvement on the single investigator assessment in a previous similar study [8], and independent review in this current study found that a handful of trials were wrongfully included as they were not within scope of the RA-COS.

One potential limitation was the variability in the quality of trial information available from different data providers [16]. While all data providers indexed on the WHO-ICTRP are acceptable publically accessible trial registration databases according to the International Committee of Medical Journal Editors (ICMJE) [17], it was clear that many entries do no strictly adhere to the 21 minimum item trial registration dataset [18], which in this study meant that some trials were excluded from the assessment. When considering reported results, trial publications and trial results were notably more easily accessible on ClinicalTrials.gov than all other registries. Despite this limitation, assessing the uptake of a COS using trials taken from a trial registry entry is preferable to citation analysis, which is the only other method we have identified as having been used to assess the uptake of a COS [19]. That approach was also applied to the RA-COS, but it proved unreliable because few of the reports of the trials that measured the COS cited the relevant publication [19].

### **Implications for practice**

In this evaluation, four different measures of uptake were calculated which relied on planned outcomes to be measured which were listed on the trial registry and reported outcomes taken from different sources. In a practical sense, researchers may only look to report on one measure which provides a reasonable estimate of COS uptake. The gold standard measure of uptake might be seen to be the first measure listed in Box 1 that relies on reported outcomes from completed studies that were identified from the trial registry. This method requires the most work to obtain the uptake estimate, as all publications and trial results from the registry need to be found and read. In this evaluation this measure of uptake provided the highest level of uptake, which might be expected as outcome data taken from trials registries might be incomplete. This is shown in Figure 1 where uptake reported from ‘results’ was always higher than ‘planned’. This was often a result of some trials only registering the primary outcome in the trial registry. Despite this, the difference in uptake statistics across all four measures was less than 10% and, assessment of uptake using reported results only may not be practical if there are relatively few trials in the field and/or the COS was only recently published. As a compromise, one of the alternative planned uptake measures from Box 1 may be satisfactory for the assessment of COS uptake.

In connection with the uptake strategy, we recommend that COS developers should have an implementation plan and that the COS uptake assessment should be done to identify if there are any barriers to uptake. In order to promote COS uptake further, we also strongly recommend that trial registries should refer to COS in their guidance on outcome selection, currently this is only implemented on the ISRCTN registry for which there was only one eligible trial in this assessment [20]. COS are also endorsed by some funders of trials, for example, in the UK, the National Institute for Health Research – Health Technology Assessment programme recommend that established COS are used in their guidance for funding [21]. Such endorsements may help promote the use of COS, particularly for non-industry funded studies [22].

**Conclusions**

It is important that COS are adopted in order to increase consistency in outcomes measured across trials and to ensure that trials are more likely to measure outcomes that are relevant to all stakeholder groups. The assessment of COS uptake is important for quantifying this COS adoption. In this RA-COS assessment, the uptake rate in published articles was maintained at just over 80% in the decade leading up to 2019. Our overarching conclusion remains similar to that in the previous evaluation of RA-COS uptake [8]: that assessing uptake using trials identified from trial registries is an efficient, reliable and up-to-date method. For the RA-COS at least, the uptake results from looking at ClinicalTrials.gov alone and all data providers listed on the WHO-ICTRP were markedly similar although the fact that a large majority of trials were registered on the former may have been influential. When considering which platform to use, those wishing to assess COS uptake should make a judgement on whether a ‘reasonable estimate’ of uptake can be achieved by looking at a single data provider or a larger sample with geographic diversity obtained from multiple data providers. A similar decision should be made on which uptake measure to use. This decision may be influenced by the number of trials available in the condition of interest, the length of time since the COS was published or both.

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**Conﬂict of interest statement:**

PRW and MC are members of the COMET (Core Outcome Measures in Effectiveness Trials) Management Group. MB, LH, JJK and KP declare no conflicts of interest.

**Authors’ Contributions:**

JJK conceived the study and is the guarantor. JJK, MC, and PRW designed the study methods. MB, LH and KP identified the relevant studies and assessed the uptake of the core outcomes from each study, while JJK verified these tasks independently. MB, LH, JJK and KP analysed the data. JJK prepared the initial manuscript. All authors were involved in the revision of this manuscript. All authors read and approved the final manuscript.

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