Journal of Clinical Epidemiology 113 (2019) 86–91

ORIGINAL ARTICLE

A cross-sectional audit showed that most Cochrane intervention reviews searched trial registers

Slavica Berber[a,1], Ava Grace Tan-Koay[a,1], Newton Opiyo[b], Kerry Dwan[b], Julie M. Glanville[c], Toby J. Lasserson[b], Melina L. Willson[a,*]

[a]*Cochrane Breast Cancer Group, Systematic Reviews and Health Technology Assessments, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*

[b]*Editorial & Methods Department, Cochrane Central Executive, London, UK*

[c]*York Health Economics Consortium, University of York, York, UK*

Accepted 22 May 2019; Published online 28 May 2019

Abstract

Objective: The objective of this study was to assess current Cochrane Review practice in identifying and incorporating information from clinical trial registers.

Study Design and Setting: A cross-sectional study was conducted to assess a sample of new or updated intervention reviews from all Cochrane Review Groups up to February 1, 2017. Two assessors independently extracted data from each review using a pretested audit questionnaire. Data were analyzed relating to the frequency of reporting (1) the register source and search strategy; (2) the results of trial register searches; and (3) the use of trial register information in the review.

Results: Over 90% (236/260) of Cochrane Reviews reported searching a trial register (e.g., ClinicalTrials.gov or the WHO International Clinical Trials Registry Platform). In reviews that reported trial register searches, 39% (92/236) indicated the number of trial records retrieved and 56.8% (134/236) used information from the trial register records in the review. Trial record information was incorporated into the results (39.6%; 53/134), risk of bias assessments (53.7%; 72/134), and discussion (24.6%, 33/134) and conclusion sections (25.4%, 34/134).

Conclusion: Most audited reviews used trial register information. Guidance may be needed to better incorporate information from these valuable resources in Cochrane Reviews to assist future research decisions made by funders and prospective study investigators.

Keywords: Registries (MeSH); Clinical trial registers; Systematic reviews; Cross-sectional study; Reporting quality; Database searching

1. Introduction

Clinical trial registers fulfill an important function by providing a transparent scientific record of clinical trials. They have been generally defined as online systems, such as Clinical Trials.gov, that provide the public with access to summary information about ongoing and completed clinical trial activity in health and medical research (as cited in [1]). Their role has been widely acknowledged as being a mechanism for reducing publication bias and detecting the misreporting of study outcomes by trialists [1–5]. The value of clinical trial registers has been strongly supported by the International Committee of Medical Journal Editors, and some governments have requested that clinical trialists detail their data-sharing statements and related documents (e.g., study protocols) in trial registration records [6] and report

Both A.G.T.-K and S.B. have dual roles and also work for the Australian New Zealand Clinical Trials Registry (ANZCTR).

Conflict of interest: None of the authors have conflict of interests or competing interests.

Funding: A.G.T.-K., S.B., and M.L.W. are supported by the NHMRC Australia for their Cochrane work and receive in-kind support from the NHMRC Clinical Trials Center, University of Sydney. N.O., K.D., and T.J.L. are employees of the Cochrane Central Executive, who provided support for their participation in this project. J.M.G. is an employee of York Health Economics Consortium, who provided support in-kind for her participation in this project.

[1] Both are considered as joint first authors.

* Corresponding author. NHMRC Clinical Trials Centre, The University of Sydney, Locked Bag 77, Camperdown, NSW 1450, Australia. Tel.: +61 2 9562 5081; fax: +61 2 9565 1863.

E-mail address: Melina.Willson@ctc.usyd.edu.au (M.L. Willson).

https://doi.org/10.1016/j.jclinepi.2019.05.020

What is new?

Key findings

- Ninety percent of a sample of published Cochrane Reviews searched clinical trials registers as part of the review process.

What this adds to what was known?

- There is increasing focus on the role that clinical trials registers can play in the conduct of systematic reviews.
- Details about completed studies obtained from trial register records can help to inform judgments about a study's risk of bias and confidence about the overall strength of evidence in a systematic review.
- Information about ongoing studies obtained from trial registers can help to inform judgments about the remaining uncertainties on a topic, inform research priorities and plans for updating systematic reviews.

What is the implication and what should change now?

- Guidance may be needed to help systematic review teams search trial registers and to make better use of information from trials register records. Evaluations of how trial registers can inform future research decisions and living systematic reviews are needed.

their trial results (using resources such as ClinicalTrials.gov; Food and Drug Administration Amendments Act of 2007 [FDAAA801—https://clinicaltrials.gov/ct2/manage-recs/fdaaa]). For systematic reviewers, these changes to trial registers may present a further impetus to encourage use of trial register information in evidence evaluations. Trial registers may become particularly useful in the conduct of living systematic reviews where searches and associated new evidence are continuously incorporated into the systematic review.

There is a keen interest in the research community concerning the impact of clinical trial registration status and trial register data on systematic review findings. To date, this has included examining whether trial registration status (i.e., registered or not) is associated with risk of bias assessments in systematic reviews with results suggesting that trials can be at high risk of bias irrespective of trial registration status [7]. In addition, several reports have reviewed the impact of searching a trial register on existing systematic reviews and reported finding eligible trials, an increase in the number of participants and data available for existing reviews, and a change in the weight of studies in the recalculated meta-analysis [8]. Overall, however, data derived from clinical trial registers did not change the direction or the statistical significance of the results in the meta-analysis in two published examples [8,9].

The importance of incorporating clinical trial register searches in systematic reviews is acknowledged by systematic review conduct and reporting standards including those developed by Cochrane and PRISMA [10,11]. Cochrane's Methodological Expectations of Cochrane Intervention Reviews (MECIR) was first introduced in 2011 and mandates searching of the WHO International Clinical Trials Registry Platform (ICTRP) portal, ClinicalTrials.gov, and other relevant trials registers to "reduce the risk of publication bias and identify as much relevant evidence as possible" (Conduct standard C27). The reporting of the search terms (not strategies) in register searches remains as a highly desirable but not mandatory feature in the 2018 MECIR standards (Reporting standard R39; [10]). Recent reports indicate that there is currently little guidance on how to incorporate clinical trial register information in systematic reviews [12], and in some fields, there has been little change in the number of systematic reviews searching clinical trial registers over the years (e.g., [13]). The extent to which Cochrane Reviews search and report their findings from clinical trial registers is unknown. Therefore, it is important to evaluate Cochrane Review compliance to the relevant MECIR standard and to record how Cochrane authors incorporate trial register information into their reviews.

In this project, our aim was to audit the current practice of searching and reporting clinical trial register searches and incorporating trial register information in Cochrane systematic reviews. A secondary aim was to assess whether guidance is required for Cochrane Review authors on how to best incorporate trial register information into the evidence evaluations.

2. Methods

We conducted a cross-sectional audit of Cochrane intervention reviews.

2.1. Selection of Cochrane Reviews

The five most recent intervention reviews published by 52 Cochrane Review Groups (CRGs) were retrieved from the Cochrane Library using the "Browse Reviews" function by Cochrane Review Group (https://www.cochranelibrary.com/browse-by-review-group), sorted by publication date. The intervention reviews or review updates were downloaded on February 1, 2017.

2.2. Auditing questionnaire

A pilot questionnaire was developed by all authors and tested by three assessors (S.B., A.G.T.K., and M.L.W.) on a subset of 20 Cochrane Reviews using a template in a Microsoft Access Database. The final version of the

questionnaire is available in Supplementary File 1. The questionnaire was divided into three parts based on the procedural aspects of the systematic review process. It covered (1) reporting the source and strategy to search for trial register information, (2) reporting the results of the trial register searches, and (3) incorporating trial register information in the review. This latter aspect included any direct reference of a trial register record or outcome from trial registry searches in the methods, risk of bias assessment, results of the review (e.g., in the abstract, plain language summary, results of the search, effects of interventions, and discussion), authors' conclusions, and GRADE assessments.

Six assessors were assigned to extract data on a set number of reviews (ranging from 20 to 110 reviews per assessor) in an independent manner, ensuring each Cochrane Review was assessed by two assessors. Assessors who were based at the Cochrane Breast Cancer Group or authored reviews did not audit their reviews. All data were imported into Excel and two assessors were responsible for resolving any data discrepancies produced by the duplicate data extraction process; if necessary, data were crosschecked against the review.

2.3. Terms and definitions

The term "trial register" had a broad meaning, and in the context of this project, it could refer to ClinicalTrials.gov, the WHO ICTRP, any register listed as a primary register in the WHO Registry network (e.g., ISRCTN [UK]), subject-specific trial registers (e.g., Stroke Trials Registry), drug company trial registers, or other potential sources of trial information which are not strictly registers (e.g., European Medicines Agency [EMA], Physician Data Queries [PDQ]).

A "search strategy" was defined as a combination of at least two terms using Boolean operators. Searches that did not use Boolean operators were classified as using "search terms" only.

For the purpose of this audit, a "trial record" referred to a trial registration record within a trial register, with or without an associated identification number. This is because, in some cases, a trial registration number was not listed in the Cochrane Review but it was evident that the Cochrane authors had used information from a clinical trial register (e.g., for risk of bias assessments). In addition, Cochrane authors sometimes used the terms "clinical trial protocol" and "trial record" interchangeably. A clinical trial protocol was judged to be synonymous with a trial record when it was determined that the review authors were not referring to a trial protocol published in a journal.

The term "eligible record" was an all-encompassing term used to refer to a trial record reported anywhere (i.e., text or tables) in the Cochrane Review. This record could be located in sections of the Cochrane Review such as results of the search, included studies, ongoing studies, excluded studies, studies awaiting classification, discussion, abstract, reference list, and characteristics of included studies and risk of bias tables.

Table 1. Proportion of reviews searching a trial register

Source searched	*n/N*	%
ClinicalTrials.gov	216/236	91.5
WHO ICTRP	203/236	86.0
Primary registry in the WHO Registry network, for example, ISRCTN (UK)	114/236	48.3
Drug company trial registers	17/236	7.2
Subject-specific trial registers (e.g., Stroke Trials Registry)	12/236	5.1
Other sources (e.g., EMA, Physician Data Queries, Centre Watch)	24/236	10.2

2.4. Data analysis

Data analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Qualitative free-text information collected in part (3) of the questionnaire was reviewed and categorized into the relevant mandatory section and subsection in the Cochrane Review (i.e., abstract, plain language summary, methods, results of the search, risk of bias assessment [in text or tables], effects of interventions, discussion, authors' conclusions, GRADE assessments, and any other section [e.g., Appendix]). For these categorized qualitative data and quantitative data, proportions and percentages were calculated.

3. Results

Of the 260 reviews identified from the 52 CRGs, 133 (51.2%) were new reviews and 127 (48.8%) were review updates. These reviews were published between January 2013 and February 1, 2017.

3.1. Reporting the source and strategy when searching trial registers

Over 90% (236/260) of Cochrane Reviews reported searching and/or contacting relevant trial registers. The most frequently searched sources were ClinicalTrials.gov (91.5%, 216/236) and the WHO ICTRP (86%, 203/236) (Table 1);

Table 2. Location of information from eligible trial records in Cochrane reviews

Section of the review	*n/N*	%
Results (narrative, i.e., results of the search and included studies)	33/51	64.7
Ongoing studies[a] table	34/51	66.7
Excluded studies table	24/51	47.1
Studies awaiting classification[b] table	13/51	25.5
Other (e.g., PRISMA flowchart, included studies reference list)	5/51	9.8

[a] Studies that are ongoing and meet (or appear to meet) the eligibility criteria of the review.

[b] Potentially relevant studies that have been identified but cannot be assessed for inclusion until additional data or information is obtained.

Table 3. Review sections where trial register information was reported

Section of the review	n/N	%
Abstract (authors' conclusions)	12/134	9.0
Plain language summary	4/134	3.0
Methods	18/134	13.4
Results—risk of bias assessment	72/134	53.7
Results—results of the search, ongoing studies	53/134	39.6
GRADE assessment	3/134	2.2
Discussion	33/134	24.6
Authors' conclusions	34/134	25.4
Published notes and appendix	4/134	3.0

most reviews reported searching both registers (81.8%, 193/236). At least one national or regional trial register was searched in almost half (48.3%, 114/236) of all reviews that conducted a search of trial registers. Two-thirds of the reviews (62.3%, 147/236) reported search strategies or terms. Of those, 117 (79.6%, 117/147) reported search strategies, 26 (17.7%, 26/147) reported search terms, and 4 (2.7%, 4/147) reviews reported both search strategies and terms.

3.2. Reporting the results of trial register searches

Among the reviews that reported searching trial registers, 39.0% (92/236) indicated the total number of trial records retrieved via the search, mainly in the PRISMA flowchart or results section. The average number of trial records screened by Cochrane authors per review was 201 (SD 565.4). Of those reviews that retrieved records, 55.4% (51/92) found eligible trial records for the review; the average number of trial records deemed eligible per review was 7 (SD 10.3).

Table 2 describes the location of information from eligible trial records in the review as reported by Cochrane authors. Eligible trial records were frequently listed in the ongoing studies tables (66.7%, 34/51) and in the narrative description of trial records and studies identified for the review (64.7%, 33/51).

3.3. Utilizing trial register information in Cochrane Reviews

In the 236 reviews that reported searching clinical trial registers, 56.8% (134/236) used information from the trial records in the review. Table 3 highlights the diverse use

Table 4. Examples of the utilization of clinical trial register information in the Discussion or Conclusion section of Cochrane Reviews

Discussion or Conclusion section	Narrative examples
Overall completeness and applicability of the evidence	• "The fact that six ongoing studies at the time of this review indicates an increased interest in this area by researchers … of the importance of conducting research in vulnerable populations" • "The risk of publication bias was minimized by searching for … trial registries, and by contacting agencies involved in this intervention" • "We would need 1,492 participants to have an 80% chance of detecting, as significant at the 5% level, an increase in all-cause mortality from 3% to 6%. The ongoing studies are planning to recruit 530 participants and therefore we may not be able to answer this review's primary outcome even when the ongoing studies have been completed"
Quality of the evidence	• "Neither of the included studies provided information on whether they were following an a priori protocol. Neither had been registered"
Potential biases in the review process	• "We could not find the results of another completed study, retrospectively registered on the WHO ICTRP… which may have met our inclusion criteria" • "Clinicaltrials.gov and WHO ICTRP yielded only two completed but unpublished studies" • "We have searched in several different databases, including trials registers, and we have hand-searched reference lists to identify eligible studies. It is nevertheless still possible that we have missed relevant material"
Agreements and disagreements with other studies or reviews	• "A search of clinical trial registries at the time of writing (…) found no registered or ongoing RCTs comparing … methods with more widely used methods"
Implications for practice	• "Ongoing studies in this area may have an influence on future practice" • "Findings from two ongoing relevant studies and the two trials for which only abstracts are available will be important in future updates of this review" • "The largest studies to date have used … Ongoing studies in this area may have an influence on future practice …"
Implications for research	• "At present, one ongoing study is investigating …. specifically in people with …. The rationale for undertaking a trial enrolling this subgroup of participants is not clear" • "We will monitor the progress of these [ongoing] trials and on publication (assuming eligibility), we will include them in future updates of this review" • "There is a need to further explore the long-term benefit and safety profile of … The ongoing, and as yet unpublished trials, will possibly satisfy these issues" • "The seven ongoing studies and the two studies awaiting assessment identified during our search also have small sample sizes and assess a wide variety of outcomes with different outcome measures…"

and reporting of information from clinical trial records in Cochrane Reviews.

Clinical trial record information was most frequently used in the assessment of risk of bias of the included studies (53.7%; 72/134), especially when judging the risk of selective outcome reporting (98.6%; 71/72). A nominal number of reviews (5.6%; 4/72) also used clinical trial record information to determine whether allocation concealment, blinding of participants and personnel, and blinding of outcome assessment were done by trialists, and the funding source of the trial. Fewer than 14% (18/134) of reviews explicitly reported in the methods section that they would use clinical trial registers to assess reporting biases.

The results section of reviews also reported trial register information with nearly 40% (53/134) of reviews referring to the status of ongoing studies on the evaluated topic. These scenarios ranged from (a) stating that no relevant ongoing studies were noted, (b) reporting the number of ongoing studies or studies awaiting classification (usually with an identification number) and the anticipated end date and sample size of the ongoing study, and (c) reporting the exclusion of studies which, in one case, was due to the study not being prospectively registered.

A quarter of the reviews used trial register information in the Discussion section (24.6%, 33/134), mostly to describe the overall completeness and applicability of the evidence (48.5%, 16/33) and potential biases in the review process (30.3%, 10/33). Table 4 presents a selection of narrative text extracted from the audited reviews. In addition, Cochrane authors referred to ongoing studies/trial register records in the authors' conclusions—implications for research section, in a quarter of those reviews that described searching clinical trial registers. In this section, the ongoing studies information was used to (a) highlight that ongoing studies might provide answers to the remaining questions in the review, (b) indicate the plan for future updating of the review by monitoring the completion of ongoing studies, and (c) indicate where future trials on the topic would be most useful. A small proportion (9%, 12/134) of reviews used the abstract conclusions to alert readers that ongoing studies at the time of publication would be available for future versions of the review.

4. Conclusions

Based on an audit of 260 reviews, Cochrane Reviews routinely searched clinical trials registers although the reporting and use of register information in the reviews is variable. Over 90% of Cochrane Reviews searched a clinical trials register, predominately the WHO ICTRP and ClinicalTrials.gov, indicating high compliance to Cochrane MECIR standards [10]. This high compliance is markedly different to the frequency of clinical trial register searches in systematic reviews in specialist areas where it ranges from 4% to 52% of reviews (e.g., pharmaceutical treatments [8]; obstetrics and gynecology [14]; pregnancy and childbirth [15]; anesthesiology [13]). In our audit, of those reviews that used clinical trial register information in some form (56.8%, 134 reviews), the most common scenarios were in judging risk of bias for selective outcome reporting, indicating the number ongoing studies, placing completed studies in the context of ongoing research activity (i.e., Discussion section), and using knowledge of ongoing studies to inform priorities for future research on the evaluated topic. Register information from drug companies or condition-specific registers were rarely reported in our sample of reviews and this may reflect that searching such resources is not stipulated in Cochrane MECIR standards. The examples provided in Table 4 highlight different ways that information from clinical trial registers can inform the discussion of evidence summarized by systematic reviews.

Apart from assessing how clinical trial registers are used in Cochrane Reviews, we were also interested in gauging whether guidance on better use of clinical trial register information was needed for systematic review teams. Based on our findings, guidance might help systematic review author teams to make better use of clinical trial registers in relation to (1) the assessment of selective outcome reporting against registry records of included studies alongside other details of study design (such as methods for allocation concealment and blinding), (2) using data in cases where the clinical trial register offers trial results, (3) to help inform GRADE decisions on publication bias, (4) describing the overall completeness of the body of evidence by referring to the number and/or planned sample size of ongoing studies and how these studies may increase certainty of findings in updating the review, (5) to encourage author teams to develop implications for future research that take account of ongoing studies enabling study investigators and research funders to focus research effort on well-established uncertainties, and (6) to indicate the plan for future updating of the Cochrane Review.

With initiatives such as the Reward Alliance [16] highlighting the volume of research waste, Cochrane Review Groups and authors could rely more heavily on clinical trial register information (in addition to conventional literature databases) to assess whether a review update is truly needed or whether a new review is actually needed.

In this audit, two-thirds of the reviews reported search strategies or terms but one-third did not. The lack of reporting of search strategies/terms and the number of search results from the trial register searches was not unexpected and is currently a highly desirable feature, not mandatory, in Cochrane Reviews. Better compliance with MECIR needs to be encouraged. The challenges of adequately searching trial registers have been well documented, ranging from concerns of suboptimal search interfaces to limited restrictions in disease categories on offer in trial registers to capture mostly relevant studies [1,17,18]. Although based on a small sample in this audit, these challenges were noted by the high number

of trial records screened (when reported), on average, by Cochrane authors. As clinical trial registers will become the hub of reporting trial results and data-sharing plans (noted in the ICJME's data-sharing statement [6]) and new machine learning approaches to searching registers are already in development [19], it is expected that these concerns relating to search efficiency and yield will be better understood and resolved in the future.

Our audit contributes to the growing body of knowledge relating to the importance of clinical trial registers and their role in systematic reviews [20]. They could act as important mechanisms for surveillance and help inform decisions to plan additional primary research and to update systematic reviews. A first step for prospective study investigators and their funders is to learn about existing studies before deciding to initiate new research. Future work that examines the merits and feasibility of trial register surveillance could examine how this might affect both conventional and living systematic reviews.

CRediT authorship contribution statement

Slavica Berber: Data curation, Methodology, Validation, Writing - original draft, Writing - review & editing. **Ava Grace Tan-Koay:** Data curation, Formal analysis, Methodology, Software, Writing - original draft, Writing - review & editing. **Newton Opiyo:** Data curation, Methodology, Writing - original draft, Writing - review & editing. **Kerry Dwan:** Data curation, Methodology, Writing - original draft, Writing - review & editing. **Julie M. Glanville:** Methodology, Supervision, Writing - original draft, Writing - review & editing. **Toby J. Lasserson:** Conceptualization, Data curation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Melina L. Willson:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing.

Acknowledgments

The authors would like to acknowledge and thank their peer reviewers. We are grateful for the in-kind support provided by the NHMRC Clinical Trials Centre, the University of Sydney, and support from the NHMRC.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2019.05.020.

References

[1] Isojarvi J, Wood H, Lefebvre C, Glanville J. Challenges of identifying unpublished data from clinical trials: getting the best out of clinical trial registers and other novel sources. Res Synth Method 2018;9:561–78.

[2] Becker JE, Krumholz HM, Ben-Josef G, Ross JS. Reporting of results in ClinicalTrials.gov and high-impact journals. JAMA 2014;311:1063–5.

[3] Hartung DM, Zarin DA, Guise JM, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med 2014;160:477–83.

[4] Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol 1986;4:1529–41.

[5] Stern HM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997;314:640.

[6] Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials: a requirement of the international committee of medical journal Editors. Ann Intern Med 2017;167:63–5.

[7] Farquhar CM, Showell MG, Showell EAE, Beetham P, Baak N, Mourad S, et al. Clinical trial registration was not an indicator for low risk of bias. J Clin Epidemiol 2017;84:47–53.

[8] Baudard M, Yavchitz A, Ravaud P, Perrodeau E, Boutron I. Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of meta-analysis. BMJ 2017;356:j448.

[9] Wilson LM, Sharma R, Dy SM, Waldfogel JM, Robinson KA. Searching ClinicalTrials.gov did not change the conclusions of a systematic review. J Clin Epidemiol 2017;90:127–35.

[10] Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological expectations of cochrane intervention reviews (MECIR) version 1.07. Available at: https://community.cochrane.org/mecir-manual. Accessed January 11, 2019.

[11] Moher D, Shamseer L, Clark M, Ghersi D, Liberati A, Petticrew M, et al, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

[12] Boden C, Bidonde J, Busch A. Gaps exist in the current guidance on the use of randomized controlled trial study protocols in systematic reviews. J Clin Epidemiol 2017;85:59–69.

[13] Yerokhin VV, Carr BK, Sneed G, Vassar M. Clinical trial registries are underused in the pregnancy and childbirth literature: a systematic review of the top 20 journals. BMC Res Notes 2016;9:475.

[14] Bibens ME, Chong AB, Vassar M. Utilization of clinical trial registries in obstetrics and gynecology systematic reviews. Obstet Gynecol 2016;127(2):248–53.

[15] Umberham BA, Detweiler BN, Sims MT, Vassar M. Clinical trial registry use in anaesthesiology systematic reviews. Eur J Anaesthesiol 2017;34:797–807.

[16] The Reward Alliance. 2015. Available at https://www.thelancet.com/campaigns/efficiency/statement. Accessed January 11, 2019.

[17] Glanville JM, Duffy S, McCool R, Varley D. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? J Med Libr Assoc 2014;102(3):177–83.

[18] Ogino D, Takahasi K, Sato H. Characteristics of clinical trial websites: information distribution between ClinicalTrials.gov and 13 primary registries in the WHO registry network. Trials 2014;15(1):428.

[19] Lanera C, Minto C, Sharma A, Gregori D, Berchialla P, Baldi I. Extending PubMed searches to ClinicalTrials.gov through a machine learning approach for systematic reviews. J Clin Epidemiol 2018;103:22–30.

[20] Bashir R, Surian D, Dunn AG. Time-to-update of systematic reviews relative to the availability of new evidence. Syst Rev 2018;7(1):195.