

CLINICAL TRIAL REGISTERS AS A SOURCE OF TRIALS FOR COCHRANE REVIEWS

DUFFY S¹, MCCOOL R¹, GLANVILLE J¹, BLACKHALL K²

¹York Health Economics Consortium, University of York, York, UK

²Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, London, UK



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BACKGROUND & OBJECTIVES

Since July 2005 all member journals of the International Committee of Medical Journal Editors (ICMJE) have required that clinical trials must be registered in a public trials register before they are considered for publication. Such registration ensures that trial details are available to all researchers, including systematic reviewers, irrespective of the results, which may encourage improvements in trial methods and minimise publication bias. The introduction of the ICMJE requirement is likely to have contributed to an increasing number of trials being registered in resources such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). There is interest in the extent to which such registers can now be relied upon as a source of trials for Cochrane systematic reviews.

Objectives:

- To explore the current state of trial registration;
- To assess whether it is adequate to search for trials, for inclusion in systematic reviews, using only public trials registers rather than major bibliographic databases such as MEDLINE;
- To explore search approaches for trial registers.

METHODS

We investigated:

- Whether included studies in two recently updated Cochrane Injuries Group Reviews were registered in ClinicalTrials.gov (CT) and International Clinical Trials Registry Platform (ICTRP);
- Whether the search strategies (search terms) reported in the reviews would have identified those registry studies in the registers.

Identifying included studies: We collated the bibliographic details of included studies from each review, and then retrieved additional study details (trial number/unique identifier, trial name, lead investigator, location, sponsor) through searches of PubMed and Google.

Having retrieved this information we then searched CT and ICTRP for the included studies using the following approaches:

Trial number identifier
OR
Trial name/abbreviation
OR
Intervention
OR
Author/lead investigator

If we did not have a trial number identifier, we included the geographical location in the search in order to limit the search results.

Trial Register Searches: We took the MEDLINE search strategies reported in the Cochrane reviews and translated them for both registries to see whether the included studies would have been identified. We undertook several search approaches to investigate how different the results might be, by adapting the original MEDLINE search strategy from each review into:

- A **highly precise** strategy (busy searcher); using just one term for the named intervention;
- A **precise** strategy; combining specific condition terms AND specific intervention terms;
- A **sensitive** strategy using only **intervention terms** (specific and generic);
- A **sensitive** strategy using **disease/condition** AND the **intervention terms** (specific and generic).

Search Analysis: We then analysed each search approach for the number of records retrieved and the number of studies included in the Cochrane review which were retrieved

COCHRANE REVIEWS

Review One

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD001886. DOI: 10.1002/14651858.CD001886.pub4.

Review Two

Henry DA, Carless PA, Moxey AJ, O'Connell D, Ker K, Fergusson DA. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD003602. DOI: 10.1002/14651858.CD003602

RESULTS

Review One (252 included studies):

- 4 were identified in CT;
- 8 were identified in ICTRP (4 unique);
- 4 trials were identified in both CT and ICTRP.

Studies with trial number identifier indexed in PubMed:

- 2 from CT (one of the published articles was not indexed at all in PubMed);
- 2 of the 4 uniquely identified trials in ICTRP (all 4 studies were available in PubMed).

Many of the 252 included studies preceded the July 2005 ICMJE decision. All of the 8 trials identified in CT/ICTRP were published post-2005. However, 46 post-2005 studies were published and could not be identified in either CT or ICTRP.

Review Two (14 included studies):

- 1 was identified in CT;
- 1 was identified in ICTRP (2 records);
- The same study was identified in both CT and ICTRP.

This study was available in PubMed, but did not have a trial number identifier in the SI field. This is unsurprising as the study was published in 1991.

Trial Register Searches: Review One

	ClinicalTrials.gov		ICTRP	
	Basic Search option	Advanced search option	Basic Search option	Advanced search option
Highly precise strategy	158 (4 included) Sensitivity 100% Precision 2.5%	149 (4 included) Sensitivity 100% Precision 2.7%	13 (1 included) Sensitivity 25% Precision 7.7%	4 (0 included) Sensitivity 0% Precision 0%
Sensitive strategy (Intervention only)	176 (4 included) Sensitivity 100% Precision 2.3%	165 (4 included) Sensitivity 100% Precision 2.4%	128(8 included) Sensitivity 100% Precision 6.2%	106 (8 included) Sensitivity 100% Precision 7.5%

NOTE: The original review search used intervention terms only, so the precise and sensitive search options could not be tested.

Trial Register Searches: Review Two

	ClinicalTrials.gov		ICTRP	
	Basic Search option	Advanced search option	Basic Search option	Advanced search option
Highly precise strategy	43 (0 included) Sensitivity 0% Precision 0%	36 (0 included) Sensitivity 0% Precision 0%	33 (1 included) Sensitivity 100% Precision 3.0%	12 (1 included) Sensitivity 100% Precision 8.3%
Sensitive (Intervention only)	45 (0 included) Sensitivity 0% Precision 0%	37 (0 included) Sensitivity 0% Precision 0%	34 (1 included) Sensitivity 100% Precision 3.0%	164 (1 included) Sensitivity 100% Precision 0.6%
Sensitive (Condition+Intervention)*	83 (1 included) Sensitivity 100% Precision 1.2%	27 (1 included) Sensitivity 100% Precision 3.7%	34 (1 included) Sensitivity 100% Precision 3.0%	2 (0 included) Sensitivity 0% Precision 0%

NOTE: In the original search the condition and intervention terms were very similar: "autologous blood" AND "blood transfusion", so the precise strategy could not be tested.

DISCUSSION

Our main objective was to explore the current state of trial registration and to then assess whether it would be possible to search for trials, for inclusion in systematic reviews, using only public trials registers rather than major bibliographic databases such as MEDLINE. From our preliminary exploration of two recently updated Cochrane reviews (based on a similar topic), the answer is that current trials registration seems to be sparse and we could not rely on trials registries in preference to searching major bibliographic databases.

As almost all of the included studies in the two reviews were unavailable in both CT and ICTRP, it was not worth considering the impact of excluding unregistered trials, as this is self evident. Even the majority of those studies published post-2005 were unregistered, so we could not rely on the registries to identify recently completed and ongoing trials. A considerable number of those post-2005 published trials were published in journals which do not publish in English (or are conducted in countries other than those in the western English speaking world: US, Canada, Australia and the UK). However, we note that the ICTRP is an international registry which includes registered trials from, among others, the Chinese Clinical Trial Registry, Brazilian Clinical Trials Registry, Iranian Registry of Clinical Trial, and Japan Primary Registries Network.

There are a number of reasons why so many of the included studies in both reviews were not identified in either CT or ICTRP. Firstly our preliminary results are derived from two reviews on similar topics. There is every possibility that a wider investigation of more Cochrane reviews, in different topic areas, will produce different findings. There is also a possibility that, despite trial results from these reviews being published post-2005, many trials had begun long before 2005, and this might explain why they have not been registered in a public trials registers.

We investigated search approaches in the two trials registries to explore how sensitive searches performed in comparison with more precise searches, and how the registers' Basic search options compared with the Advanced search options. Further investigation is warranted, because the search strategies used in Review One were already very sensitive, using only search terms for interventions. Although Review Two did combine conditions and interventions search terms, these terms were very similar, and it was difficult to translate the search to run effectively in the relatively unsophisticated search interfaces available in CT and ICTRP. It would be useful to investigate more extensive and complex search strategies and assess how those strategies might work using the search options available in these, and other, trial registers.

Exploring a wider range of reviews (and search strategies) will enable us to gain a better picture of the overlap between trials registries, and whether it is possible to restrict to searching one or two registries, or whether we need to look further afield. We will also be able to investigate whether increasingly a greater proportion of trials are being registered.

CONTACT DETAILS

York Health Economics Consortium Limited
Level 2, Market Square
University of York
York, YO10 5NH
United Kingdom

Tel: 44-1904 324832
email: steven.duffy@york.ac.uk
<http://www.yhec.co.uk>