NCCHTA

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RAPID REVIEWS FOR THE HTA PROGRAMME

Ongoing trials in Technology Assessment Reviews

Protocol for a methodology review

A. Details of review team

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B. Full title of research question

Identification and assessment of ongoing trials in health technology assessment reviews (TARs)

C. Clarification of research question and scope

In this research, *ongoing trials* (or trials in progress) are defined as any trials that have started but results are not yet available or only interim results available for technology assessment reviews (TARs). There may be different reasons for results of relevant trials not available when a TAR is being conducted. For example, the results may not be available because studies have not been completed, or have been completed but results have not been published or disclosed.

Identification and consideration of ongoing clinical trials is very common in TARs. According to the list published on the NICE website by September 5th 2001, the number of completed TARs is 27. By checking the executive summary of these completed TARs, eight TARs have encountered ongoing trials. The actual number of TARs that have identified ongoing trials will be greater if the full reports are examined. Even if the TARs have not identified or considered ongoing trials, that may not mean there are no ongoing trials.

It may not be surprising that there are many ongoing trials in TARs. Health technologies evaluated in TARs are often recently developed. The effectiveness and cost-effectiveness of health technologies can rarely be confirmed by a single trial or a few trials. A series of trials may have to be carried out (phase I - IV) for a new health technology.

Ongoing trials should be considered seriously in TARs for several reasons. First, available evidence has suggested that there may be time lag bias or 'pipeline effect': the speed of publication depends on the direction and strength of the trial results.[1,2] For example, studies with significant results may have been published earlier than those with non-significant results.[3] Second, large-scale trials are often following early small trials. The conclusions based on limited evidence from early small trials may be easily overturned by more convincing evidence from later large-scale trials. Thirdly, ongoing trials may be designed particularly to answer important clinical or policy questions that have not been investigated in previous trials. Fourthly, awareness of ongoing trials will be helpful to make recommendation about when a completed TAR should be updated and about need for further research.[4]

There may be mainly two methodological issues about ongoing trials in TARs: identification of ongoing trials and assessment of possible impact of ongoing trials on the conclusions and recommendations.

Identification of ongoing trials

There are many different sources for identifying ongoing trials (such as trials registers; experts; investigators; trial sponsors). The importance of ongoing trials has been recognised and many registers of trials (including planned or ongoing trials) have been established.[1,4,5] For example, ongoing trials can be identified from UK National Research Register, and metaRegister of Controlled Trials. Design and early results of trials may also be presented at conferences or meetings. Thus conference proceedings or journal supplements may also sources of ongoing trials.

Identification of all relevant ongoing trials may not be an easy and simple task. For example, Manheimer and Anderson reviewed public information about ongoing trials funded by industry.[6] They concluded that "existing trials registers are unlikely to be meeting user needs since many ongoing trials are not listed". For searching and identifying ongoing trials, current guidelines for systematic reviews have not provided detailed recommendations. The available guidelines (such as CRD's and the Cochrane handbook) are mainly about the search and location of published trials. There is a need to summarise, assess and develop the search strategies for identifying ongoing trials. In addition, a list of registries of clinical trials in a previous HTA review of publication and related biases[1] needs to be updated.

Assessment of potential impact of ongoing trials

From identified trial protocols, registration summaries or abstracts of ongoing trials, it may be possible to obtain useful information about trial objectives, sample size, patient inclusion/exclusion criteria, interventions compared, outcome measures, length of follow-up, and even early findings. This information may help to assess the potential impact of ongoing trials.

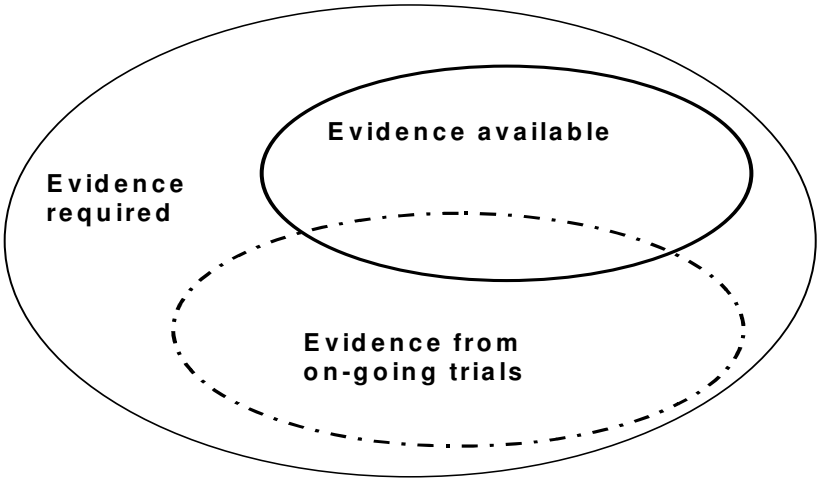
Decisions made based on the existing trials may be altered when the results from ongoing (or unpublished) trials become available. For example, the results of ongoing trials may :

- improve the precision of estimates of effectiveness and cost-effectiveness;
- overturn conclusions, that is, positive results become equivalent or negative, or negative results become equivalent or positive;

- answer research questions that have not been considered in previous trials (eg, different population, different settings/intervention strategies, different outcomes, etc)

The possible impact of ongoing trials should be assessed according to (1) evidence that is required to make clinical and policy decisions; (2) evidence that is already available; and (3) features of ongoing trials (Figure). If the available evidence is from many large scale trials and the number and scale of ongoing trials is very limited, then the possible impact of ongoing trials may be ignorable. On the other hand, if the number and scale of ongoing trials is substantial (relative to the available trials), then the impact of ongoing trials will be considerable. In this case, ongoing trials may yield data that could overturn the effectiveness estimate based on the evidence currently available.

The possible impact of ongoing trials may be estimated according to the quantity and quality of the available trials versus the quantity of ongoing trials. The quantity of trials could be measured by using the number of trials and/or patients (events). According to the quantity of ongoing trials, the robustness of estimated effect size based on the available trials may be tested by sensitivity analyses. For example, if the treatment effect based on the available trials is small or moderate, it could easily disappear due to more negative results from ongoing trials. On the other hand, a great effect based on many completed trials may be less likely disappear by including negative results from ongoing trials.



Some methods used to consider whether to conduct a trial may be adapted to estimate the possible impact of ongoing trials.[7,8] Other methods that are possibly useful include certain methods for detecting publication bias,[1] methods for cumulative meta-analysis,[9] or methods for investigating heterogeneity in meta-analysis (with or without modification).[10] Bayesian approaches to predictions or decision making seem to be particularly useful in this context.[11-13] There is a need to summarise and assess methods or approaches for assessing possible impact of ongoing trials in TARs.

Proposed research scope and objectives

This research aims to assess the importance of ongoing trials in reviews of health technology assessment, and to provide practical recommendations for identifying ongoing trials and assessing the possible impact of ongoing trials in TARs. More specifically, this research aims to:

1. review the identification and assessment of ongoing trials in the completed TARs
2. summarise sources of ongoing trials, and recommend good search practice for identifying ongoing trials
3. identify and evaluate methods for assessing the impact of on-going trials

D. Report Methods

This research will include:

1. a review of relevant literature,
2. an assessment of ongoing trials in TARs completed by the end of August 2002,
3. a survey and assessment of trial registers and other sources of ongoing trials,
4. a summary and assessment of available methods for assessing the impact of ongoing trials.

Literature review

Identifying studies

Thr following electronic databases will be searched to identify relevant literature: Medline, the Cochrane Library (Methodology Register and reviews) and the UK National Research Register. Strategies that will be used to search these electronic databases are presented in Appendix 1 .

It has been recognised that literature search for methodological studies is much more difficult because of less well defined boundaries and inappropriate indexation in commonly used databases.[14] Thus it is anticipated that an iterative approach will be used, by checking

bibliography of retrieved studies and contacting experts in the fields. The Science Citation Index will be used to identify studies that cited key references.

Selected journals, abstracts presented at Systematic Review Symposia (1998 to 2002) or Society for Clinical Trials Meetings (1980 to 2002) will be handsearched. Appendix 2 shows a list of key journals, books and conference proceedings that will be handsearched for relevant studies.

Criteria for inclusion

References identified by the literature search will be assessed for inclusion independently by two reviewers. Any disagreement will be solved by discussion or a third reviewer. Studies will be included if they are relevant in terms of

- methods that can be used to estimate the impact of missing or ongoing studies in meta-analyses of systematic reviews,
- methods for identifying ongoing studies,
- empirical evidence about importance of ongoing trials,
- development, assessment and utilization of prospective registration of trials.

Survey and assessment of registers and other sources of ongoing trials

Based on those TARs which identified and assessed ongoing trials and newly identified sources, an updated list of trial registries will be provided. The major trial registries will be assessed according to various criteria eg accessibility, completeness and characteristics of trials included. An evaluation form has been developed for this task (Appendix 3).

Other sources of ongoing trials (eg, conference abstracts) will also be summarised and assessed.

Assessment of completed TARs

All published TARs by the end of August 2002 will be included (**n=47**). The included TARs will be assessed in terms of:

- major characteristics of interventions evaluated;
- quantity and quality of identify clinical research;
- TAR conclusions;
- recommendations for future research;
- whether and how ongoing trials have been searched;

- whether the ongoing trials have been identified;
- whether and how the impact of ongoing trials have been assessed and considered.

This will provide empirical evidence about the importance of ongoing trials and methods for their identification and evaluations. For simplicity, we will focus on the impact of ongoing trials on the effectiveness of health technologies, unless the main purpose of ongoing trials is to assess cost-effectiveness. Appendix 4 is the form that will be used to extract data from completed TARs.

The methods for identifying ongoing trials and estimating their possible impact will be assessed and illustrated in 2-4 selected TARs. The selection of examples will depend on the methods to be tested. If ongoing trials have not been searched in the selected TARs, we may conduct a search to check whether there are ongoing trials. For TARs in which ongoing trials have been identified and assessed, the impact of ongoing trials will be summarised.

Evidence synthesis

Based on the above review of theoretical research and empirical evidence, we will provide practical recommendations for identifying and assessing ongoing trials in TARs, and provide recommendations for future research.

E. Handling the company submission(s)

Not applicable

F. Project Management

a. **Timetable/milestones**

Final protocol:	End of November 2002
Completing literature search:	End of January 2003
Completing assessment of identified methodology studies	End of February 2003
Completing assessment of published TARs:	End of March 2003
Progress report:	End of March 2003
Completing review of trial registry	End of March 2003
Completing case studies:	End of April 2003
Draft report for peer review	End of May 2003
Final report	End of June 2003

b. **Competing Interests**

None

c. **External reviewers**

Will be identified and supplied with the progress report.

Reference List

1. Song F, Eastwood A, Gilbody S, Duley L, Sutton A. Publication and related biases. *Health Technology Assessment* 2000;**4 (10)**.

2. Olsen, K. L., Hopewell, S., Dickersin, K., Clarke, M., and Oxman, A. D. Publication bias in clinical trials. (Issue 3). 2002. Update Software Ltd. The Cochrane Library.

3. Hopewell, S., Clarke, M., Stewart, L., and Tierney, J. Time to publication for results of clinical trials. (Issue 3). 2002. Update Software Ltd. The Cochrane Library.

4. Chalmers I. Using systematic reviews and registers of ongoing trials for scientific and ethical trial design, monitoring, and reporting. In Egger M, Davey-Smith G, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context*, pp 429-43. London: BMJ Books, 2000.

5. Dickersin K. Report from the panel on the Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials. *Controlled Clin Trials* 1988;**9**:76-81.

6. Manheimer E,.Anderson D. Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and acessibility. *BMJ* 2002;**325**:528-31.

7. Carpenter LM. Is the study worth doing? *Lancet* 1993;**342**:221-3.

8. Parmar MKB, Ungerleider RS, Simon R. Assessing whether to perform a confirmatory randomized clinical trial. *Journal of the National Cancer Institute* 1996;**88**:1645-51.

9. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *J Clin Epidemiol* 1995;**48**:45-57.

10. Song F, Sheldon TA, Sutton AJ, Abrams KR, Jones DR. Methods for exploring heterogeneity in meta-analysis. *Evaluation & the Health Professions* 2001;**24**:126-51.

11. Fletcher A, Spiegelhalter D, Staessen J, Thijs L, Bulpitt C. Implications for trials in progress of publication of positive results. *Lancet* 1993;**342**:653-57.

12. Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomized trials. *J R Statist Soc A* 1994;**157**:357-416.

13. Claxton K, Neumann PJ, Araki S, Weinstein MC. Bayesian value-of-information analysis: an application to a policy model of alzheimer disease. *International Journal of Technology Assessment in Health Care* 2001;**17**:38-55.

14. Edwards S, Lilford RJ, Kiauka S. Different types of systematic review in health services research. In Black N, Brazier J, Fitzpatrick R, Reeves B, eds. *Health services research methods: a guide to best practice*, pp 255-9. London: BMJ Books, 1998.

Appendix 1: Strategies to search electronic databases

A strategy will be developed based on the following concepts of the search question: Ongoing trials; trials registers and systematic review methodology. A pilot search of MEDLINE has been run and the following terms identified for each concept:
Ongoing trials: Ongoing trial$.tw.; ongoing clinical trial$.tw.; ongoing drug trial$.tw.; trial$ in progress.tw.; clinical trial$ in progress.tw.; protocol$.tw.; phase I.tw.; phase II.tw.; phase III.tw.; phase IV.tw.; Exp clinical trials/; exp controlled clinical trials/
Trial registers: registries/; trial register$.tw.; trial registries; trial registration.
Systematic review methodology: meta-analysis/; review literature/; meta-analys$.tw.; systematic review$.tw.; data synthesis.tw.

The final strategy will be devised iteratively with terms being added and/or removed as appropriate. It will then be adapted for use in the National Research Register.

The Cochrane Database of Methodology Reviews will be searched to establish whether there are any existing Cochrane reviews or protocols for reviews relating to the methodology of searching for and using ongoing trials in systematic reviews. The Cochrane Methodology Register will be searched for reports of empirical studies on these same methodological topics. It is proposed that the following CMR index terms will be used : Study identification – general; study identification – search strategies – trials; study identification – prospective registration – trials; study identification – internet; study identification – publication bias.

Appendix 2: List of key journals, books and conference proceedings that will be handsearched

Key journals (from 1990 to 2002):

- Controlled Clinical Trials (1980-2002)
- Journal of Clinical Epidemiology (1990-2002)
- Statistics in Medicine (1990-2002)
- International Journal of Technology Assessment in Health Care (1990-2002)

Books or reports:

- Egger M, Davey-Smith G, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2000.
- Black N, Brazier J, Fitzpatrick R, Reeves B, eds. *Health services research methods: a guide to best practice*, pp 255-9. London: BMJ Books, 1998.
- Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R. The advanced handbook of methods in evidence based healthcare. Sage Publications, 2001.
- Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. John Wiley & Sons, 2000.
- Cooper H, Hedges LV (ed). The handbook of research synthesis. New York: Russell Sage Foundation, 1994.
- CRD's guidance for those carrying out or commissioning reviews- undertaking systematic reviews of research on effectiveness. The University of York. 2001.
- Cochrane reviewers' handbook 4.1. Oxford: The Cochrane Collaboration 2000.

Conference abstracts:

- Systematic Review Symposium, Oxford, UK (1998 to 2002)
- Cochrane Collaboration Colloquiums (1992-2002)
- Society for Clinical Trials Meetings (1980 to 2002)
- The International Society of Technology Assessment in Health Care (1990 to 2002)

Appendix 3: Evaluation Form for Registers of Ongoing Trials

Name of source: _____

Location/url: _____

Date of evaluation: _____

General

Sponsors/Producers: _____

Type of info e.g. full protocol, abstract only, title only: _____

Diseases/interventions covered: _____

Multinational or national ☐ Multinational ☐ National

Comments: _____

_____

Accessibility: _____

Completed or ongoing trials ☐ Completed ☐ Ongoing ☐ Both

Proportion of trials in progress: _____

Specific info about trials

Study ID	☐ Yes	☐ No
Title	☐ Yes	☐ No
Summary of purpose	☐ Yes	☐ No
Recruitment status	☐ Yes	☐ No

Study type & design: _____

Sample size	☐ Yes	☐ No
Patient incl/excl criteria	☐ Yes	☐ No

Interventions compared ☐ Yes ☐ No

Outcomes ☐ Yes ☐ No
Length of follow-up ☐ Yes ☐ No
Location of study ☐ Yes ☐ No

Who is conducting the study: _____

Information identification/retrieval

General layout appearance: _____

Ease of navigation: _____

Help feature ☐ Yes ☐ No

Comments: _____

_____

_____

Links to other sources ☐ Yes ☐ No

Comments: _____

Search facilities:

Keywords ☐ Yes ☐ No
Index terms ☐ Yes ☐ No
Phrases ☐ Yes ☐ No
Boolean ☐ Yes ☐ No
Truncation ☐ Yes ☐ No
Limits ☐ Yes ☐ No

Comments: _____

_____

_____

Full text ☐ Yes ☐ No

Speed/response time: _____

Currency: _____

Frequency of Updating: _____

Exporting facilities:

Mark records	☐ Yes	☐ No
Record format	☐ Yes	☐ No
Download to disc	☐ Yes	☐ No
Email	☐ Yes	☐ No
Print	☐ Yes	☐ No

Reviewer:_____ Date:_____ Appraisal No:_____

Appendix 4: Ongoing trials in completed TARs - data extraction form

Title:_____

_____

Authors:_____

Source:_____

Intervention evaluated:_____

Type of intervention: ¨ Drug; ¨ Surgical; ¨ Educational/counselling; ¨ Diagnostic/screening; ¨ Other _____

Date licensed for use in UK: _____ ¨ Unknown; ¨ Not applicable

Patients/Participants: _____

Outcome measures: _____

No. of trials included: RCT ___; non-RCT ___; Cohort studies ___; Case-series ___; Other_____

How were the studies combined: ¨ Descriptive; ¨ Meta-analysis; ¨ Other_____

TAR main conclusions (effectiveness): _____

_____

_____

_____

Sources searched to identify relevant studies:

¨ Medline ¨ Embase ¨ CINAHL ¨ PsycLIT
¨ References ¨ Experts/company ¨ Sci Cit Index ¨ NRR
¨ CCT/mRCT ¨ PDQ ¨ ClinicalTrials.gov ¨ Cochrane Lib(+CCTR & DARE)
¨ SIGLE ¨ Conference abstracts

¨ Others: _____ _____

_____ _____

Was the search of ongoing trials explicit? ¨ No; ¨ Yes; ¨ Not sure

Any relevant ongoing trials identified? ¨ No; ¨ Yes If yes, no. of ongoing trials_____

Reviewer:_____ Date:_____ Appraisal No:_____

Any attempts to estimate the impact of ongoing trials? ☐ No; ☐ Yes; ☐ Not sure; ☐ Not applicable

If yes, ☐ Narrative; ☐ Quantitative; ☐ Other _____

If quantitative, method(s) used: _____

What were the possible impact? ☐ Available; ☐ Not Available; ☐ Not sure; ☐ Not applicable

If available, nature of the possible impact (more than one can be selected):

☐ Internal validity ☐ Precision/power ☐ Generalisability
☐ Different comparators ☐ Different patients ☐ Different settings
☐ Variant intervention ☐ Different outcomes

☐ Other_____

Any impact of ongoing trials on TAR's conclusions? ☐ No; ☐ Yes

If yes, more details: _____

_____

_____

Any research recommendations related to ongoing trials ? ☐ No; ☐ Yes

If yes, more details: _____

_____

To be selected as a case study? ☐ Not suitable; ☐ Not sure; ☐ Possible; ☐ Recommended

Your comments or notes: _____

_____

_____

_____

Included trials (Completed or with interim results)

Intervention	Comparator	Indications (patients, 1st or 2nd line etc)	Design	No. of studies	No. of patients	Format (eg, published, abstract or industry submission)

Ongoing trials identified

Intervention	Comparator	Indications (patients, 1st or 2nd line etc)	Design	No. of studies	No. of patients	Source (eg, trial registry, conference abstract, etc)	Any interim results?