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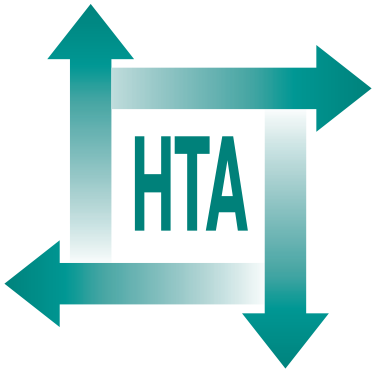

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Identification and assessment of ongoing trials in health technology assessment reviews

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Abstract

Identification and assessment of ongoing trials in health technology assessment reviews

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Objectives: To assess the importance of ongoing trials in health technology assessment reviews (HTARs) for the National Institute for Clinical Excellence and to provide practical recommendations for identifying ongoing trials and assessing their possible impact.

Data sources: Electronic databases.

Review methods: Ongoing trials (or trials in progress) were defined as any trials that have started but where the results are not yet available or only interim results are available for HTARs. This methodological review included: (1) an assessment of ongoing trials in HTARs completed by the end of August 2002, (2) a survey and assessment of trial registers and other sources of ongoing trials and (3) a summary and assessment of available methods for assessing the possible impacts of ongoing trials.

Results: The identification of ongoing trials is a common phenomenon in reviews of health technology assessment. Twenty-three of the 32 HTARs identified one or more ongoing trials and in eight of these the information on identified ongoing trials was not considered in the evidence synthesis and research recommendations. All but one HTAR that considered the potential impact of ongoing trials adopted a narrative approach. Trial registers and grey literature are important sources of information on ongoing trials. All 32 HTARs explicitly or implicitly searched for unpublished studies, and/or ongoing trials and/or grey literature and trial registers. The assessment of six commonly used trial registers suggested that most registers provided sufficient information for reviewers to decide the relevance of identified ongoing trials. However, it is sometimes extremely difficult to know whether ongoing trials identified from different sources (registers) are the same trials or belong to the same multicentre trials. The ISRCTN (the International Standard Randomised Controlled Trial Number) is the most reliable system but it has not been widely adopted. The qualitative assessment of ongoing trials compared major features of completed and ongoing trials, providing information about the possible impact of ongoing trials in terms of relevance, validity, reliability and generalisability. Quantitative methods to assess the impact of ongoing trials include cumulative meta-analysis related methods, fail-safe N, Bayesian data monitoring, and Bayesian interim predictions. The most useful method may be the Bayesian predictive probability, which estimates predictive probabilities for any possible values of treatment effect. A case study indicated that the appropriate use of quantitative methods would strengthen findings from narrative assessment of possible impact of ongoing trials.

Conclusions: Identification of ongoing trials is common in HTARs. Searching for ongoing trials in effectiveness reviews should be more thorough and explicit. Conversely, primary researchers, in particular those working with in multicentre trials, should label ongoing trials more clearly, preferably by ISRCTN. Qualitative assessment of identified ongoing trials is crucial and informative. Available quantitative methods could be used to strengthen findings from narrative assessment, although further research and more empirical examples are required. Information from ongoing trials may contribute to syntheses of results, conclusions and recommendations for future research. Future research is suggested into the identification and assessment of ongoing trials in other systematic reviews of effectiveness of health care interventions; existing and new methods for incorporating information on ongoing trials; comparing estimated impacts with the actual results of ongoing trials; and to incorporate findings from the assessment of ongoing trials into decision models.

Contents

List of abbreviations

5-FU	5-fluorouracil
ASCO	American Society of Clinical Oncology
BANDY	Bayesian Analysis using Normal Distributions
CHD	coronary heart disease
CI	confidence interval
CIS	cumulative information size
CLL	chronic lymphocytic leukaemia
CRD	Centre for Reviews and Dissemination
ESRC	Economic and Social Research Council
EU	European Union
FA	folinic acid
FDA	Food and Drug Administration
GIST	gastrointestinal stromal tumour
HTAR	health technology assessment review
ICRP	International Cancer Research Portfolio
ISRCTN	International Standard Randomised Controlled Trial Number
MeSH	Medical Subject Headings
MRC	Medical Research Council
*m*RCT	*meta*Register of Controlled Trials
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
NLM	National Library of Medicine
NRR	National Research Register
OIS	optimal information size
RCT	randomised controlled trial
ReFER	Research Findings Electronic Register
UKCCCR	UK Register of Clinical Trials in Cancer
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background and objectives

Clinical and policy decisions on healthcare interventions have to be made according to the best currently available evidence. However, the evidence base evolves over time. Knowledge about the existence of ongoing trials and considering their possible impact on research evidence will help decision-makers to understand how confident or tentative their decisions must be. The awareness and assessment of ongoing research may result in more appropriate decisions about whether and when a completed health technology assessment review (HTAR) should be updated. Any recommendations for further trials should also consider trials in progress. This research aims to assess the importance of ongoing trials in HTARs for the National Institute for Clinical Excellence and to provide practical recommendations for identifying ongoing trials and assessing their possible impact.

Methods

Ongoing trials (or trials in progress) were defined as any trials that have started but where the results are not yet available or only interim results are available for HTARs. This methodological review included: (1) an assessment of ongoing trials in HTARs completed by the end of August 2002, (2) a survey and assessment of trial registers and other sources of ongoing trials and (3) a summary and assessment of available methods for assessing the possible impacts of ongoing trials.

Ongoing trials in the completed HTARs

The identification of ongoing trials was found to be a common phenomenon in reviews of health technology assessment. Twenty-three of the 32 HTARs identified one or more ongoing trials. This phenomenon was not clearly associated with any HTAR characteristics, such as disease or technology categories, explicitness of search strategies, convincingness of HTAR conclusions and number of studies included. In eight of the 23 HTARs with ongoing trials, the information on identified ongoing trials was not considered in the evidence synthesis and research recommendations. Of the remaining 15 HTARs with ongoing trials, 12 attempted to consider the impact of ongoing trials on conclusions, eight on research recommendations and only three HTARs with ongoing trials incorporated information on ongoing trials in the results synthesis. All but one HTAR that considered the potential impact of ongoing trials adopted a narrative approach.

Sources of and searching for ongoing trials

Trial registers and grey literature are important sources of information on ongoing trials. There are a large number of trial registers (international or national, general or subject-specific). The assessment of six commonly used trial registers suggested that most registers provided sufficient information for reviewers to decide the relevance of identified ongoing trials. However, it was sometimes extremely difficult to know whether ongoing trials identified from different sources (registers) were the same trials or belonged to the same multicentre trials. The ISRCTN (the International Standard Randomised Controlled Trial Number) is the most reliable system but it has not been widely adopted. All 32 HTARs explicitly or implicitly searched for unpublished studies, and/or ongoing trials and/or grey literature and trial registers. The efforts made to search for unpublished trials or grey literature may result in the identification of ongoing trials. Case studies indicated that a search of additional sources may identify additional ongoing trials.

Methods for assessing the impact of ongoing trials

The qualitative assessment of ongoing trials compared major features of completed and ongoing trials, providing information about the possible impact of ongoing trials in terms of relevance, validity, reliability and generalisability. All quantitative methods that may be used to assess the impact of ongoing trials require subjective judgement about levels of Type I and II

error, minimal clinically worthwhile benefit, and presumed prior distribution of the parameter. The fail-safe N method and Bayesian data monitoring method do not directly use information on ongoing trials, but focus on the assessment of the conclusiveness of existing evidence. The number of patients in ongoing trials may be useful for estimating optimal or cumulative information size for cumulative meta-analysis-related methods (sequential monitoring boundaries and stochastic curtailment method). The most useful method may be the Bayesian predictive probability, which estimates predictive probabilities for any possible values of treatment effect. A case study indicated that the appropriate use of quantitative methods would strengthen findings from narrative assessment of possible impact of ongoing trials.

Conclusions

Identification of ongoing trials is common in HTARs. Searching for ongoing trials in effectiveness reviews should be more thorough and explicit. Conversely, primary researchers, in particular those working within multicentre trials, should label ongoing trials more clearly, preferably by ISRCTN. Qualitative assessment of identified ongoing trials is crucial and informative. Available quantitative methods could be used to strengthen findings from narrative assessment, although further research and more empirical examples are required. Information from ongoing trials may contribute to syntheses of results, conclusions and recommendations for future research.

Recommendations for future research

The following areas are suggested for further research.

- Identification and assessment of ongoing trials in other systematic reviews of effectiveness of healthcare interventions (for example, Cochrane Systematic Reviews) should be evaluated.
- Existing and new qualitative and quantitative methods for incorporating information on ongoing trials need to be tested and compared in further effectiveness reviews and/or computer simulation studies.
- The validity of estimated impacts of ongoing trials could be evaluated by comparing estimated impacts with the actual results of ongoing trials. This could be done prospectively with long-term follow-up of selected HTARs. A retrospective study would also be possible by examining the evolution of trial evidence for selected topics.
- Further research is required to incorporate findings from the assessment of ongoing trials into decision models. For example, posterior predictive distribution may be useful for dealing with uncertainty problems in cost-effectiveness modelling.

Chapter 1

Background and objectives

Technology assessment reviews and ongoing trials

The National Institute for Clinical Excellence (NICE), as a special health authority for England and Wales, was established in 1999 to provide guidance on new and existing healthcare interventions (http://www.nice.org.uk/). NICE guidance is based on the appraisals of selected health technologies. The appraisals of health technology derive evidence on clinical and cost-effectiveness of health technologies from technology assessment reviews (HTARs) and submissions from consultees (Guide to the Technology Appraisal Process, NICE, 2001). The National Coordinating Centre for Health Technology Assessment (NCCHTA) commission and organise HTARs for NICE. By 15 October 2003, 68 technology appraisals were completed and 42 in progress (http://www.nice.org.uk/). Recently, the World Health Organization (WHO) Regional Office for Europe carried out a review of NICE and "was impressed by the commitment to using rigorous methodology throughout the process of technology assessment".[1]

A technology assessment review usually contains a systematic review of effectiveness and an evaluation of cost-effectiveness. As in any literature review, potential biases may be introduced if the assessment review is not systematic. Principles and guidelines for carrying out systematic reviews [as detailed in the Centre for Reviews and Dissemination (CRD) review guidance[2] or the Cochrane reviewers' handbook[3]] are also relevant for the review of effectiveness in HTARs.

While conducting HTARs for NICE, we recognised that identification and consideration of ongoing clinical trials was very common. This was further confirmed by a quick examination of the executive summaries of 27 completed HTARs on the NICE website by 5 September 2001. Eight of the 27 HTARs had encountered ongoing trials. We suspected that the actual number of HTARs that had identified ongoing trials would be greater if the full reports were examined, and, even if the HTARs had not identified or considered ongoing trials, it might not mean there were no relevant ongoing trials.

The above observation about ongoing trials is not surprising. Health technologies evaluated in HTARs for NICE are often recently developed. The effectiveness and cost-effectiveness of health technologies can rarely be confirmed by a single trial or a few trials. Usually a series of trials have to be carried out for a new health technology. We also observed that existing guidelines for systematic reviews mainly considered the search and analyses of completed studies (published or unpublished). There is a need to review the importance of ongoing trials in effectiveness reviews and to summarise methods that may be used to search for ongoing trials and methods to assess ongoing trials in effectiveness reviews.

Phases of clinical trials

To evaluate effectiveness of healthcare interventions, trials are carried out to answer a series of research questions. To some extent, the potential impact of ongoing trials may be determined by the questions the trials intend to answer. Different stages of the development of a health technology have different research questions that need to be answered by trials. Correspondingly, clinical trials can be classified into different phases. For example, Piantadosi[4] separated the development of healthcare technologies (drugs or non-pharmacological therapies) into following stages: (1) early development, (2) middle development, (3) comparative studies and (4) late development, which correspond roughly to Phase I, II, III and IV drug trials.

Early developmental studies test the mechanism of a healthcare intervention. For the development of a new drug, this early stage is featured with Phase I trials. Usually, a new drug will first be tested in Phase I trials to examine its pharmacological properties (e.g. toxicity, metabolism, absorption, elimination and safe dose range) in humans.[5] Phase I trials are usually short-term and do not involve any treatment comparison.

Based on findings from early developmental studies, **middle developmental studies** evaluate

more clinically relevant outcomes and treatment tolerability (including feasibility, safety and efficacy). These studies correspond to Phase II drug trials that aim to provide preliminary evidence about efficacy and side-effects of a new drug. The scale of Phase II trials is usually small and surrogate outcomes (e.g. changes in tumour size) are often used. According to whether a comparison treatment is involved, Phase II trials may be further classified as Phase IIa and IIb trials. Phase IIa trials are feasibility trials without controls and often use surrogate outcomes (intermediate end-points) in a small number of patients. Phase IIb trials are randomised trials using a control intervention and are similar to phase IIa trials in other aspects.

Comparative studies evaluate the relative efficacy of a new treatment by including a control group in which patients receive alternative interventions (e.g. placebo or the current standard treatment). Phase IIb and III drug trials are comparative studies. Phase IIb trials are small scale and measure intermediate endpoints. Phase III trials are full-scale evaluations using definitive endpoints (e.g. disease progression, survival) and often include a large number of patients.

Late developmental studies evaluate rare side-effects or complications and interactions with other interventions. They correspond to Phase IV drug trials or postmarketing surveillance studies. A drug may be removed from the market because of rare but severe side-effects detected by these late developmental studies.[6]

It is not unusual that promising findings of early phase trials are not confirmed by findings from larger and more rigorous comparative trials. For example, results of subsequent large-scale trials did not confirm positive results from early trials of nitrate therapy and magnesium therapy in acute myocardial infarction.[7]

Definition of ongoing trials

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

From its start to completion, a trial usually has to go through several stages: patient recruitment, data collection, interim analysis and publication of results (*Figure 1*). It usually takes many months or years for a clinical trial to be completed. Data generated by ongoing trials are usually continuously monitored by a Data and Safety Monitoring Committee. Clinical trials could be terminated early, for example, when interim analyses reveal significant differences between treatments or severe adverse effects.[4] Issues in data monitoring and interim analysis of trials are being reviewed in a project funded by the UK HTA programme (http://www.ncchta.org/project.asp?Pjtld=1144).

Clearly, a trial is ongoing if it is at the stage of patient recruitment. However, when interim results are available, a trial could be considered as completed for patients whose data are already analysed but as in progress for further patients to be included. Generally, we consider that a trial is completed when its results are formally published. After formal publication, some trials continue to follow patients up for many years so that they could be considered as being in progress for long-term follow-up data.

Ongoing studies are different from unpublished studies, although sometimes it is difficult to distinguish between the two. Unpublished trials may be considered as completed if reviewers can access trial results (for example, through industry submission). If the results of a completed trial are not available for the assessment review, it is tentatively considered as 'ongoing'. We recognise that some trial results may never be published, and for such trials 'ongoing' is not a proper label. Similarly, some ongoing trials may be terminated and never be completed. However, trials that are terminated early or unpublished may be as important as trials that are completed and published. Therefore, it is not always straightforward to decide whether a trial is ongoing or completed. A key question is whether a trial could provide **relevant** results that are not yet available. If the answer is yes, the trial is ongoing.

Importance of ongoing trials

The strength of evidence from trials can be discerned in terms of level of certainty, generalisability and precision [confidence intervals (CIs)]. Sometimes, the results of trials are classified as positive (statistically significant in favour of the treatment of interest), negative (statistically significant in favour of comparators) or equivalent

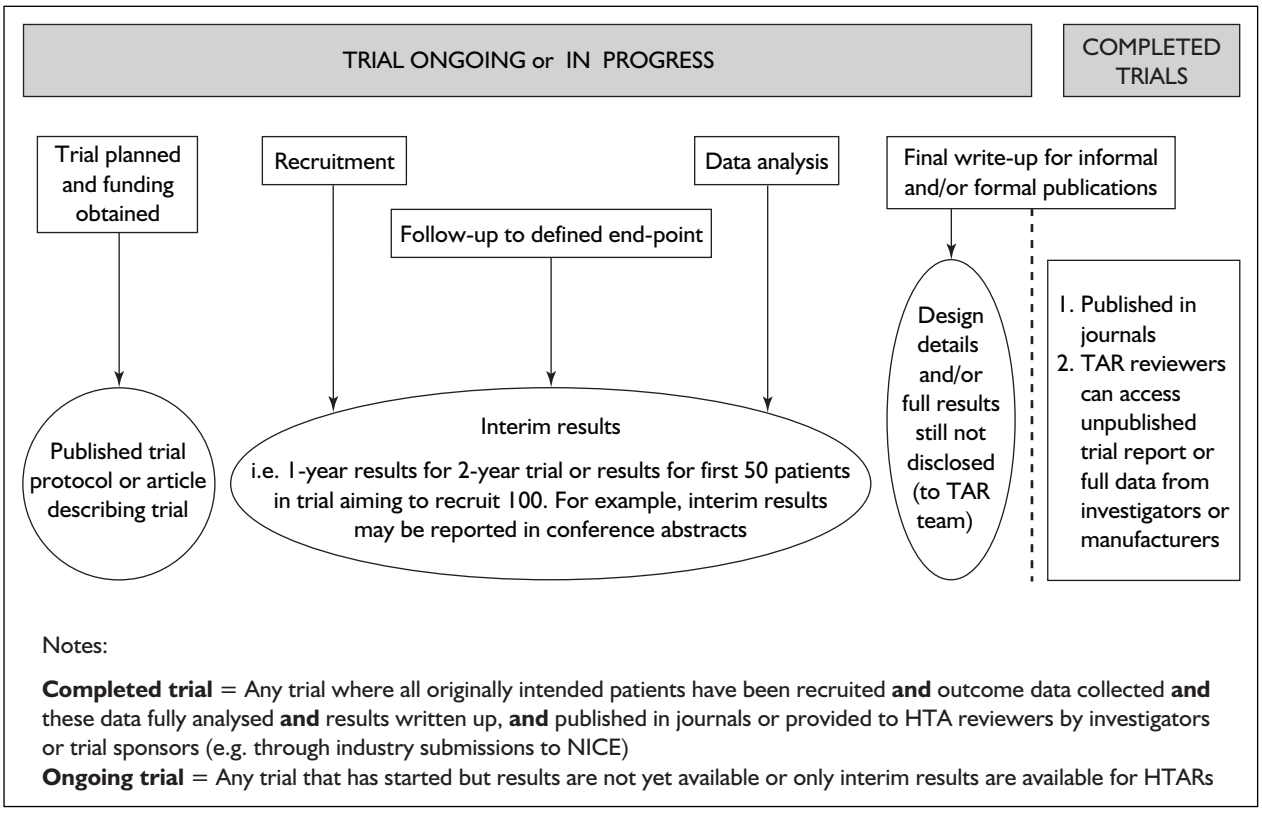

FIGURE 1 *Stages of trial – with particular reference to the definition of ongoing trial*

(no significant difference between the treatment and comparator). Since statistical significance may not be equivalent to clinical importance, the concept of 'minimal clinically worthwhile benefit' has been suggested.[8] According to the minimal clinically important difference between two competing interventions, the 'range of equivalence' can be decided.[9]

The strength of available evidence is related to changes in clinical practice. Fletcher and colleagues[8] suggested three stages of changing clinical practice: (1) there is no evidence from randomised controlled trials (RCTs); (2) RCT evidence is available but not convincing; and (3) overwhelming evidence from RCTs is available. Clearly, the importance of ongoing trials will be reduced if overwhelming evidence is already available. The evidence from ongoing trials will be crucial when there is no evidence from RCTs or the available evidence from RCTs is not convincing. To a large extent, therefore, the importance of ongoing trials will depend on the strength of the existing evidence.

Ongoing trials should be considered seriously in systematic reviews of effectiveness of healthcare interventions for the following reasons:

- Available evidence has suggested that there may be time lag bias or 'pipeline effect', where the speed of publication depends on the direction and strength of the trial results.[10,11] For example, studies with significant results may have been published earlier than those with non-significant results.[12]
- Second, large-scale trials often follow early small trials. The conclusions based on limited evidence from early small trials may be overturned by more convincing evidence from later large-scale trials.[13–15]
- Third, ongoing trials may be designed particularly to answer important clinical or policy questions that have not been investigated in previous trials.[16]
- Fourth, awareness of ongoing trials will be helpful in making recommendations about when HTARs should be updated and about need for further research.[17]

The importance of ongoing trials will largely depend on the availability and strength of the existing evidence (*Table 1*). Previous studies have focused on whether new trials should be carried out or whether the ongoing trials should be terminated given the existing evidence or new evidence.[8,18] If the existing evidence is already

TABLE 1 *Usefulness of information about ongoing trials and existing evidence*

Existing evidence	No ongoing trial	There are ongoing trials
Convincing evidence	No need for further trials	Decide whether ongoing trials should be terminated
Unconvincing evidence	Further trials recommended	Assess the impact of ongoing trials, whether uncertainty will be reduced when the results of ongoing trials become available
No adequate research evidence	Further trials recommended	Assess the impact of ongoing trials, whether the ongoing trials will provide relevant and robust evidence to answer important research questions

convincing, there will be no need for further trials and ongoing trials may be terminated. If there is no evidence or no convincing evidence, further trials will usually be recommended. If important trials are ongoing, it may be recommended that important decisions should be made only after their results are available. In many cases, although decisions are required now, diligent decision-makers will want to know about any future changes in the evidence.

Two major methodological issues

There are two main methodological issues about ongoing trials in HTARs: (1) identification of ongoing trials and (2) assessment of possible impact of ongoing trials on the conclusions and recommendations.

There are many different sources of information on ongoing trials (such as trials registers, experts, investigators and trial sponsors). The importance of ongoing trials has been recognised and many registers of trials (including planned or ongoing trials) have been established.[10,17,19,20] Ongoing trials can be identified from a variety of sources, including the *meta*Register of Controlled Trials (*m*RCT). Design and early results of trials may also be presented at conferences or meetings.

Confident identification of all relevant ongoing trials is currently not possible. For example, Manheimer and Anderson reviewed public information about ongoing trials funded by industry.[20] 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 those of the CRD and the Cochrane Handbook) are mainly about searching for published reports of trials. There is a need to summarise, assess and develop search strategies for identifying 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.

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 or patients or 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 owing to less positive results from ongoing trials. On the other hand, a great effect based on many completed trials may be less likely to 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.[21,22] Other methods that are possibly useful include certain methods for detecting publication bias,[23] methods for cumulative meta-analysis[24] or methods for investigating heterogeneity in meta-analysis.[25] Bayesian approaches to predictions or decision-making seem to be particularly useful in this context.[8,26,27] There is a need to summarise and assess methods or approaches for assessing the possible impact of ongoing trials in HTARs.

Objectives and approaches

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 HTARs. This report includes:

- a review of relevant literature
- an assessment of ongoing trials in HTARs completed by the end of August 2002
- a survey and assessment of trial registers and other sources of ongoing trials
- a review of available methods for assessing the impact of ongoing trials.

Chapter 2

Search for relevant literature

To identify potentially relevant methodological literature for this review, we systematically searched several databases. Literature searches for methodological studies are difficult because there are less well-defined boundaries and inappropriate indexing in commonly used databases.[28] An iterative approach was used. The search for relevant literature was updated iteratively by different reviewers, using more focused search strategies for given research questions. In this section, only the results of the first stage of the literature search are presented.

Methods

Databases searched

The following electronic databases were searched to identify relevant literature: MEDLINE, the Cochrane Database of Methodology Reviews and the Cochrane Methodology Register. Strategies that were used to search these electronic databases are presented in Appendix 1. Selected journals, abstracts presented at Systematic Review Symposia (1998–2002) or Society for Clinical Trials Meetings (1980–2002) were handsearched.

Criteria for inclusion

The review included studies that were relevant in terms of

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

References identified by the literature search were assessed for inclusion independently by two reviewers. Any disagreement was resolved by discussion or by a third reviewer.

Results and summary

The most useful database was the register of methodological studies in the Cochrane Library. In total, we identified 89 references that were of possible relevance to this review (see Appendix 2 for the list of these references). Of the 89 references, 33 references were potentially useful about sources of or searching for ongoing trials and 12 references were considered to be potentially useful for the review of methods for assessing the impact of ongoing trials (*Table 2*). The identified studies were assessed separately in the following relevant chapters. Researchers involved in the later chapters also searched relevant studies, for example, by checking lists of retrieved studies or citation searches based on identified key studies.

TABLE 2 *Number of references identified by literature search*

	Number of references
Sources or search for ongoing trials	33
Methods for assessing ongoing trials	12
General about publication bias	21
Other	23
Total	89

Chapter 3

Ongoing trials in health technology assessment reviews (HTARs)

Introduction

The aim of the survey of ongoing trials in completed HTARs was to gather empirical evidence about the potential importance of ongoing trials. Specifically:

- To document the frequency of occurrence of ongoing trials in recent health technology assessments (HTAs).
- To examine search strategies employed to identify ongoing trials and the rationale behind the search strategies chosen, for example, whether search strategies were influenced by the age of the technology and the quantity and quality of evidence available to HTAR teams.
- To document and comment on methods employed by HTAR teams to incorporate ongoing trials into results, conclusions and research recommendations and the rationale behind methods chosen.

Methods

To be included in this survey, a HTAR had to meet the following criteria: formally published as an HTA monograph and associated with a NICE guidance issued by the end of August 2002 (available at http://www.hta.nhsweb.nhs.uk/). Only data concerned with the effectiveness part of the review were assessed. Five reviewers were involved in data extraction, using a data extraction form that was extensively piloted (Appendix 3). Each HTAR was assessed independently by two reviewers. Two reviewers finally checked and combined the data on to a single data extraction form. Core data were transcribed to an Excel spreadsheet for the purposes of analysis (see Appendix 4). Data extraction was completed for 32 completed HTARs meeting our inclusion criteria.[29–60]

Characteristics of included HTARs

The majority of technologies being assessed by the included HTARs were drugs (n = 24) followed by surgical techniques (n = 5) and one HTAR each for devices, diagnostic tests and debriding agents. Cancer was the disease topic with the largest number of HTARs (n = 10), followed by orthopaedics (n = 4), coronary heart disease (CHD)-related diseases (n = 3), obesity (n = 3), diseases of the central nervous system (n = 2), endocrine disease (n = 2) and infectious diseases (n = 2). One HTAR each was concerned with dental disease, psychiatric disease, public health, respiratory disease, gastrointestinal disease and surgical wounds.

The total number of studies included in individual HTARs ranged from 1 to 138 (median 24). Twenty-nine out of 32 HTARs included at least one RCT. Only three HTARs relied exclusively on primary or secondary evidence from cohort studies, case series or 'other' study designs;[41,53,59] one of these HTARs was concerned with the assessment of a diagnostic test.[53]

Twenty-three out of 32 HTARs provided a narrative synthesis of results only whereas nine proceeded to a quantitative synthesis for all or some of the included studies. The method of quantitative synthesis was meta-analysis in all nine HTARS. One HTAR[30] undertook a modelling exercise to investigate the possible impact on its conclusions of three ongoing trials with no interim results.

In only eight HTARs did the authors conclude that there was convincing evidence to support or refute the use of a health technology. In the remaining 24 HTARS the conclusion could be classified as unconvincing or unclear.

Identified ongoing trials

Ongoing trials are defined as any clinical trials that have started but where the results are not yet available or only interim results are available for HTARs. One or more ongoing trials were identified in the majority (23 out of the 32) of the included HTARs. The total number of ongoing trials identified in each HTAR ranged from 1 to

94 and comprised those identified by the HTAR authors as a result of the search strategy. This included ongoing trials defined as such by the HTAR authors and ongoing trials identified by this review team as a result of the scrutiny of studies retrieved from the HTAR search strategy, both included and excluded studies. Excluded ongoing trials not referenced in the HTARs will not have been scrutinised.

Table 3 shows the HTAR category and identification of ongoing trials. The proportion of HTARs that identified ongoing trials is not clearly associated with the technologies assessed, disease categories, HTAR conclusions, number of RCTs included in HTARs or explicitness of search for ongoing trials. It should be noted that the number of HTARs involved is small and the comparison between different HTAR categories may not be reliable.

TABLE 3 *HTAR category and identification of ongoing trials in HTARs*

HTAR category	No. of HTARs identified ongoing trials/No. of HTARs
Technology category	
Drug	17/23
Surgical	5/6
Other	1/3
Disease category	
Cancer	8/10
CHD	3/3
Orthopaedics	2/4
All other	10/15
HTAR conclusions	
Convincing conclusion	6/8
Unconvincing or unclear	17/24
Search strategy	
Explicit for ongoing trials	8/11
Not explicit for ongoing trials but explicitly searched unpublished or grey literature	4/5
Not explicit for ongoing, unpublished or grey literature	11/15
Number of RCTs included	
0	2/3
1–4	6/8
5–10	3/3
11–20	6/11
>20	6/7
Total	**23/32 (72%)**

Search strategy for ongoing trials

For the purposes of this survey, search strategies are described as implicit if the search strategy included a search of sources of unpublished or ongoing trials but no explicit intention to search for unpublished or ongoing trials was stated in the review methods. Search strategies are described as explicit if the intention to search for unpublished literature and/or on-going trials is explicitly stated in the review methods and included in the search strategy. All of the 32 HTARs surveyed undertook as a minimum an implicit search for unpublished literature and/or ongoing trials. Fifteen out of a total of 32 included HTARs stated explicitly that they had searched for unpublished data and 11 had explicitly searched for ongoing trials.

The quantity of research available to HTAR teams may impact on the decision to search for unpublished literature and/or ongoing trials. It follows that HTAR teams anticipating relatively little available research may have been more likely to have had an explicit statement of intent in their methods section. *Figure 2* shows the association between the average number of studies included in individual HTARs and whether an explicit statement was made in a HTAR's methods that there had been a search for ongoing trials. It appeared that those HTARs with an explicit statement that they had searched for ongoing trials had, on average, a smaller number of included studies (20 versus 26 for all studies and 12 versus 18 for RCTs), suggesting that the quantity of research available to HTAR teams might have influenced their search strategies. In addition to the quantity of research available, the quality of research readily accessible to HTAR teams may also have impacted on whether a decision was made to search for unpublished and ongoing trials. Of the three HTARs that relied on evidence exclusively from cohort/case series or other non-experimental designs,[33,53,59] one stated explicitly in the methods that they had searched for ongoing trials[33,53,59] and two for unpublished data.[33,59] All three of these HTARs searched grey literature and/or sources of ongoing trials such as trial registers.

The proportion of HTARs identifying one or more ongoing trials was the same for HTARs that explicitly searched and those that did not explicitly search for ongoing trials (*Table 3*). In addition, there was no difference in the number of ongoing trials identified in HTARs between the HTARs that explicitly searched for ongoing trials and those that did not (*Figure 3*).

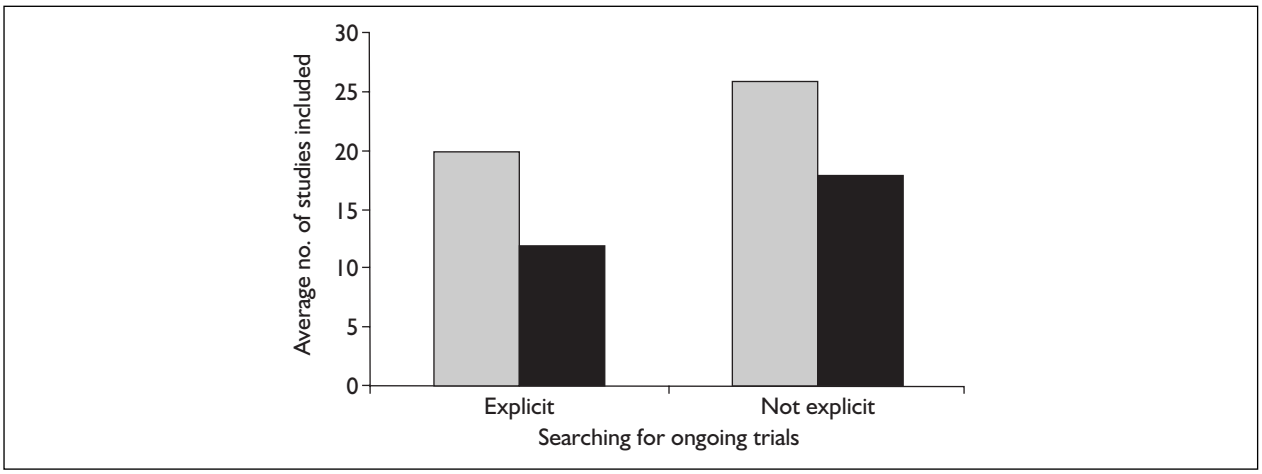

FIGURE 2 *Average number of studies included in HTARs and explicitness of searching for ongoing trials (shaded bars: all studies; black bars: RCTs).*

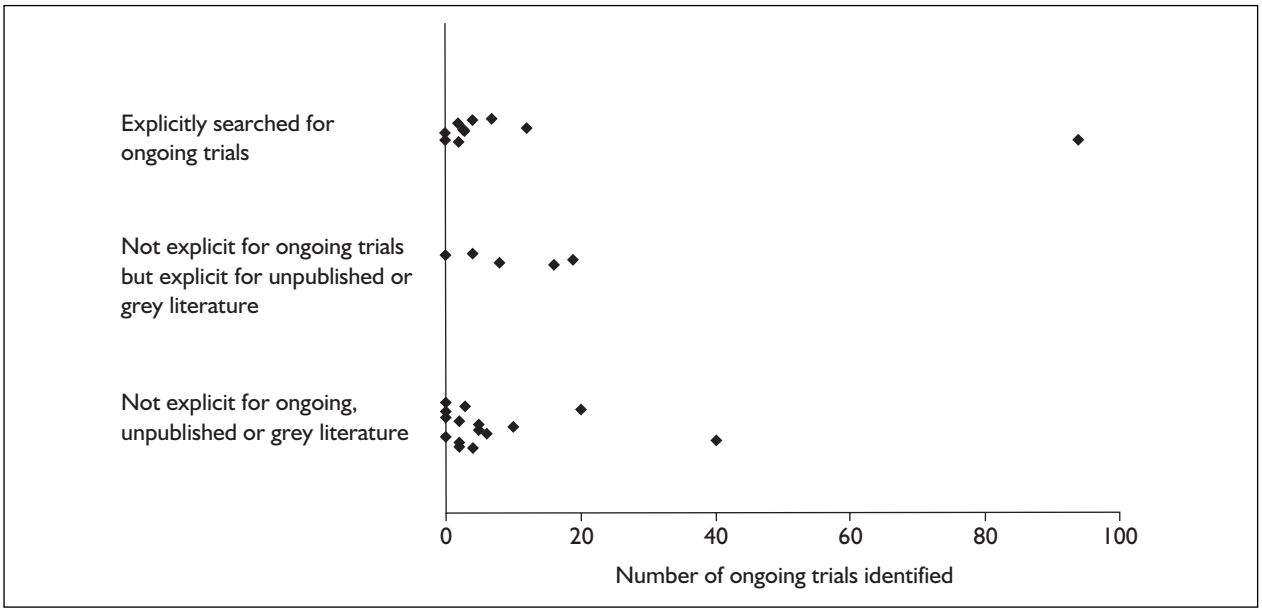

FIGURE 3 *Explicitness of searching for ongoing trials and number of ongoing trials identified*

Data synthesis

This section considers how HTAR teams have used information from ongoing trials in the synthesis of results, in drawing conclusions and in making research recommendations. In eight of the 23 HTARs that identified ongoing trials, the potential impact of ongoing trials was not included in the HTARs. In 15 HTARs the impact of identified ongoing trials was considered in some way (*Figure 4*). Only one HTAR[40] assessed the impact of ongoing trials on results and conclusions and research recommendations. Typically, the added impact of ongoing trials was considered by HTAR teams in drawing conclusions (n = 12) and in recommendations for future research (n = 8). It was rare that the impact of ongoing trials was assessed in the synthesis of results (n = 3). One HTAR undertook a quantitative assessment of the impact of ongoing trials on the HTAR results, which took the form of a sensitivity analysis to test the robustness of the overall effect size to potential negative results of three ongoing trials.[30] Two HTARs assessed the added impact of ongoing trials narratively.[40,59] When interpreting these observations, it is important to note that interim results are not a prerequisite for assessing the added impact of ongoing trials on results, conclusions or research recommendations (see Chapter 5).

Table 4 compares the total number of included studies in HTARs and whether HTAR authors considered the impact of identified ongoing trials

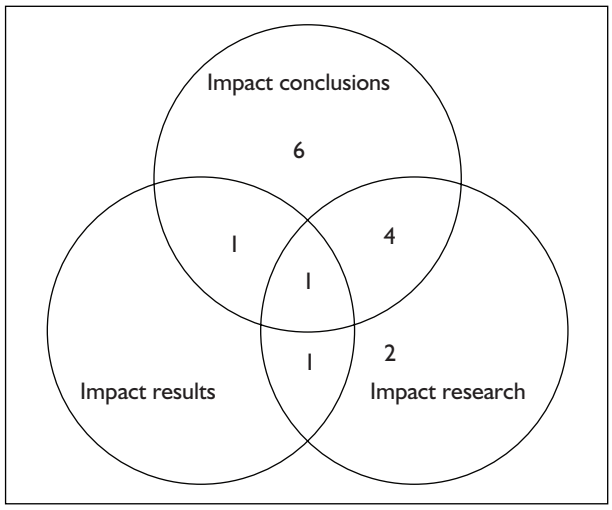

FIGURE 4 *Number of HTARs that identified ongoing trials and assessed added impact of ongoing trials on results, conclusions and research recommendations*

on one or more of their results, conclusions or research recommendations. There is a tendency for HTARs with a large number of included studies (>20) to be less likely to have considered the impact of ongoing trials identified. With respect to the quality of research available to HTAR authors, the two HTARs relying solely on evidence from cohort/case series or other non-experimental designs that also identified ongoing trials considered the impact of ongoing trials on two or more of results, conclusions and/or research recommendations.

Table 4 also illustrates the relationship between the conclusion category and the investigation of the impact of identified ongoing trials. A greater proportion of HTARs with unconvincing or unclear conclusions considered the impact of identified ongoing trials in drawing conclusions. There are no clear differences between HTARs with convincing conclusions and HTARs with unconvincing or unclear conclusions for considering the impact of ongoing trials in results synthesis and research recommendations.

Discussion

It is important to note that our definition of or conceptualisation of an 'ongoing' trial may not have been the same as the original HTAR team's definition of an ongoing trial. The concept of what constitutes an ongoing trial is evolving in parallel to an evolving appreciation of the potential impact that ongoing trials may have on HTA. However the issue of the definition of what constitutes an ongoing trial should not distort the findings of this review, as the importance of ongoing trials is distinct from how they are defined or conceptualised. The key issue is an appreciation of the importance of the literature

TABLE 4 *Some HTAR characteristics and number of HTARs that identified ongoing trials and considered the impact of ongoing trials*

	No. of HTARs considered impact of ongoing trials/ No. of HTARs identified ongoing trials		
	Impact results	**Impact conclusions**	**Impact research**
Number of any included studies			
<5	1/4	2/4	1/4
5–10	1/4	2/4	3/4
11–20	1/6	4/6	2/6
>20	0/9	4/9	2/9
Number of RCTs included			
0	1/2	1/2	2/2
1–4	1/6	4/6	2/6
5–10	0/3	2/3	1/3
11–20	1/6	3/6	1/6
>20	0/6	2/6	2/6
HTAR conclusions			
Convincing	1/6	2/6	3/6
Unconvincing or unclear	2/17	10/17	5/17
All with ongoing trials	**3/23**	**12/23**	**8/23**

regardless of publication status and regardless of whether interim results are available.

All of the HTARs surveyed included a search of grey literature and/or trial registers. Consequently, ongoing trials were identified in a large proportion of HTARs (23/32), although ongoing trials were not explicitly sought in many HTARs. There is room for improvement in the number of HTARs making explicit statements concerning searching for ongoing trials and unpublished data to facilitate the quality assessment of review methods. The importance of explicit reporting in systematic reviews is primarily to allow readers to judge the quality of the review and identify, for example, whether review methods are likely to have minimised biases. Ongoing trials are likely to be a relatively more important source of evidence in an assessment of a newer technology or when existing evidence is limited in quantity or of poor quality. As strategies for searching for ongoing trials are developed and become more commonplace as part of systematic review methods, explicit reporting of these search strategies in HTAR methods will be important in the assessment of a review's quality.

Explicit reporting of search strategies is not associated with the number of ongoing trials identified. This is not surprising as the number of ongoing trials identified will be determined by a variety of factors such as the age of the technology under assessment, the number of ongoing trials available in the topic area and specific sources of literature searched within the broad categories of 'unpublished literature', 'grey literature' or 'trial registers' (see Chapter 4). In addition, search strategies specifically designed to capture ongoing trials have only recently been developed and the number of ongoing trials databases is expanding rapidly such that even those HTARs completed in 2002 will not have had access to the volume of ongoing trial data available now.

The rationale behind searching for ongoing trials in HTARs included in this survey is not clearly linked to issues such as the quality and quantity of evidence available to HTAR authors, the HTAR disease topic area or the certainty of HTAR authors' conclusions based on published evidence. This finding probably reflects the fact that an appreciation of the potential importance of ongoing trials and methods for searching for them are still evolving.

The search strategies of 23/32 of the HTARs included in this survey identified one or more ongoing trials. Fifteen of these 23 HTARs considered the impact of the ongoing trials identified. It is possible that the quantity and quality of research available to HTAR teams included in this survey influenced whether the impact of ongoing trials was considered. The majority of HTARs (14/15) that considered the impact of ongoing trials considered the impact of ongoing trials narratively rather than adopting a quantitative approach. Only three HTARs considered the added impact of ongoing trials on their results and the majority confined their assessment to the added impact of ongoing trials on HTAR conclusions and/or research recommendations. This finding may in part be explained by the fact that the data contained in many ongoing trials are limited and, for example, may consist of a title only. In addition, methods available for quantitative estimation of the added impact of ongoing trials are in their infancy or are unknown to HTAR reviewers.

The NICE guidance associated with the included HTARs recommended that the health technology appraisal would be updated in future. There is an average of 2.5 years between the recommended date of review updating and the date of NICE guidance publication. It is interesting that the period estimated is not associated with whether there were ongoing trials identified in HTARs and

TABLE 5 *Recommendation for review updating and ongoing trials in HTARs*

	Average years between recommended review and HTAR publication
HTARs identified ongoing trials and considered impact on results (n = 3)	1.8
HTARs identified ongoing trials and considered impact on conclusions (n = 12)	2.1
HTARs identified ongoing trials and considered impact on research (n = 8)	2.5
HTARs identified ongoing trials but without considering impact (n = 10)	2.7
HTARs that did not identify ongoing trials (n = 9)	2.5
All HTARs (n = 32)	2.5

whether the possible impact of identified ongoing trials was considered (*Table 5*).

In summary, the survey presented here demonstrates that the identification of ongoing trials is a common phenomenon within HTA, although the small number of HTARs involved in this analysis does not allow a sound examination of relationships between HTAR characteristics and identification or assessment of the impact of ongoing trials. Search strategies currently employed by HTAR teams may identify ongoing trials but the thoroughness of search strategies for identifying ongoing trials currently employed needs assessment. Searching for ongoing trials should be more explicit. There is room for improvement in the use of information about ongoing trials for HTARs' conclusions and recommendations.

Chapter 4

Sources of and searching for trials in progress

Introduction

Over the years, many efforts have been made to improve access to information on ongoing trials for the benefit of both the public and the scientific community. It is often difficult to obtain information on ongoing trials because such information may be in a variety of locations and in a variety of forms – abstracts, brief references, trial protocols, patient-orientated information, via research ethics committees and so on. In this chapter, we describe sources of information on ongoing trials and assess the major characteristics of commonly used trial registers. Two case studies are used to discuss issues about searching registers of ongoing trials and some recommendations are given on formulating search strategies.

Sources of information about ongoing trials

The sources of information on ongoing trials discussed below are also summarised in Appendix 5.

Trial protocols

A trial protocol provides important information about ongoing trials, such as the characteristics of participants, interventions evaluated, outcomes measured and duration of follow-up. *The Lancet* has invited submission of study protocols by those involved in RCTs, with a provisional commitment to publish the primary clinical paper.[61] A summary of each protocol is published on the journal's website (www.thelancet.com) with contact details and the expected submission date of the primary report. The aims of this initiative include attracting good-quality research papers, contributing to a register of trials, and reducing publication bias. By mid-June 2001, *The Lancet* had received 150 protocols of which 52 had been 'accepted'. According to *The Lancet's* editorial team (personal communication), only 20–30 submissions are received each year and only about one-quarter of these are forwarded for peer review and ultimately publication, hence the apparently low activity on the site. Indeed, up to June 2003, only two new protocols had been accepted for that year. The collection may be accessed on *The Lancet's* website (see above) by clicking on 'Information for Authors' at the top of the page and then 'Protocol Reviews'.

A similar initiative has been undertaken by the publisher of online journals BioMed Central, which has invited researchers, including systematic reviewers, to publish their full protocols online. Protocols of trials and papers on the design of trials, and research reports based on trials, systematic reviews and items on methodological subjects are accessible on the BioMed Central website at www.biomedcentral.com. By selecting 'Clinical Trials' one can then choose to browse the protocols and research papers or be directed to instructions on how to submit protocols.

These recent initiatives have focused on providing researchers with both a means to publish their own trial protocols and access other people's and have followed from more general efforts to provide access to the results of these protocols, that is, the ongoing research itself. Fortunately, much progress has been made in the creation of registries and databases of ongoing trials during the past decade.

International registers of clinical trials

Clinical trial registers vary widely in purpose, content, the amount and type of information they provide. Dickersin and Rennie[62] bemoan the lack of international action in developing one comprehensive trial register and maintain that, if true progress is to be made, legislation enforcing registration of all clinical trials is essential. Nonetheless, an examination of progress to date and currently used registries illustrates the range of past and current activity undertaken in efforts to make ongoing trials more accessible to researchers and reviewers. We first discuss general trial registers that include trials in many countries.

MetaRegister of Controlled Trials

The *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) is one of the largest sources of information about controlled trials in the world, concentrating principally on trials in progress but also including some information about completed trials. The *m*RCT provides access to the contents of more than 20 major registers.[63]

In total, the *m*RCT database contains nearly 15,000 records. In addition, the Controlled Trials Links Register (CCT Links) provides more than 130 links to registers of trials on other websites, although each of these links has to be searched individually.

A bid for European Union (EU) funding to support public registration of trials using the existing Current Controlled Trials register failed.[64] As the publisher (Current Controlled Trials) had undertaken to provide open, free access to the information in the *m*RCT, from October 2002 a system of charges was introduced for those wishing to make their trial registers publicly accessible through the *m*RCT. Registers which have not agreed to this and are not updating their records are distinguished as such on the list so that searchers are aware which of the databases are not being kept up-to-date. This fact is not immediately obvious to those new to the *m*RCT, and although this was not envisaged when the register was set up, it is unfortunate that as a result of the failure to obtain funding the register is not as comprehensive or up-to-date as it was intended to be.

An important offshoot of the *m*RCT is the establishment of a unique numbering scheme for RCTs which allocates each trial its own identification number, allowing it to be tracked as time progresses.[65] The International Standard Randomised Controlled Trial Number (ISRCTN) will enable each trial (including its protocol) to be identified by a unique number. Because an application for EU funding for the scheme was rejected, Current Controlled Trials now asks trial sponsors to pay an administration charge for each ISRCTN assigned. The ISRCTN scheme was piloted by the Medical Research Council (MRC) and other trial sponsors, and journals such as the *BMJ* and *The Lancet* have agreed to participate. Trialists are increasingly being asked to obtain an ISRCTN before a trial is approved, funded or published but can apply for registration at any stage of the process.

In addition to the *m*RCT database, a second database has been added by Current Controlled Trials under the ISRCTN heading. This separate database consists solely of RCTs which have been allocated an ISRCTN. At October 2003, the ISRCTN database contained 1338 records that are not necessarily included in the *m*RCT.

TrialsCentral register of registers

Because there are many different clinical trial registers worldwide, Dickersin and Rennie set up the first international register of trial registers at Brown University in the USA in 1987.[62] This register is now available online through the TrialsCentral website (www.trialscentral.org) and covers over 200 US registers (clinical, commercial and subject-specific) and 37 international registers. The registers may be searched by medical condition or trial location and across all registers or solely US registers.

A register of registers such as TrialsCentral illustrates the difficulty of coordinating trial registration across the world, given the differences between countries, cultures and organisations, not to mention subject coverage. Tonks highlighted the dramatic variations between the various trial registers in terms of what details they record, how they are run and how accessible they are.[63] Furthermore, "registered trials seem to be a biased subset of all trials: 60% of registers are confined to AIDS or cancer trials and most cover only drug trials and not other interventions".[63]

BioMed Central

The BioMed Central site (www.biomedcentral.com) offers the facility to publish trial protocols or trial results, although, to date, relatively few have been posted. All protocols and trials are peer-reviewed before publication. To locate protocols or trials, click on 'Clinical Trials' and then 'Browse Protocols', or 'Research Papers', respectively. Full instructions to authors wishing to submit protocols are provided online.

UK-based trials and research registers

Medical Research Council (MRC)

The MRC (www.mrc.ac.uk) provides information on research that it is supporting on its own and in collaboration with other organisations. Note that MRC trials are included in the *m*RCT and should be viewed there. The website link to the MRC Clinical Trials Register links direct to the *m*RCT.

Science and Engineering Knowledge Network (SEKNeT)

SEKNeT has replaced NEST (Network for the Exploitation of Science and Technology) as the UK gateway to all Research Council databases for information on research project activity and expertise. The six organisations covered include the MRC (see above) and the Economic and Social Research Council (ESRC). It is possible to search by project information or geographical region across all or one of the sites (www.seknet.co.uk).

National Research Register (NRR)

This Department of Health website (www.doh.gov.uk/research/nrr.htm) provides a register of ongoing and recently completed research projects funded by, or of interest to, the NHS with information on over 80,000 research projects. Records on the NRR can include details on research title, research question, methodology, sample group, outcome measures and research project contacts. Projects are indexed using Medical Subject Headings (MeSH). Results are listed according to the database in which they are held. In addition to the NRR, these include the MRC clinical trials and abstracts of Cochrane reviews.

Until recently, a subset of records submitted was sent to Current Controlled Trials for inclusion in the *m*RCT. These were those records allocated the MeSH heading of randomised-controlled-trial and were submitted by the lead centre conducting the research. In effect when carrying out an all database search of the *m*RCT one would be searching RCTs on the NRR. However since the introduction of charges for contributors to the *m*RCT, NRR has become one of the databases no longer supplying updated records to Current Controlled Trials so it can no longer be assumed that a search of the *m*RCT will also cover the NRR. In addition to this factor, a separate search of the NRR website is also recommended both to allow searching for non-randomised trials and because the search facility provided on NRR is more sophisticated and includes a MeSH browser. Because the records on the NRR have been submitted by a large number of data providers, sometimes a number of records are submitted for the same project, especially in the case of multicentred trials, and it is worth being aware of the possibility of duplicate records within NRR.

NHS Trusts Clinical Trials Register

This is a new (September 2003) register of RCTs carried out in England for which the research costs have been met by the NHS. It is being supported by a 3-year contract let by the Department of Health and one of its aims is to ensure that all NHS trials are registered and assigned an ISRCTN. Trials which are only partly funded by the NHS are not included in the register, nor does it include trials which have an end date on or before 31 March 2003. The NHS Trusts Clinical Trials Register displays a minimum dataset for each trial and this is taken from records submitted to the NRR. Data collection for the register started by filtering the records submitted to the NRR in March 2003 (NRR issue 2, 2003) and the register went live in summer 2003. The NHS Trusts Clinical Trials Register is included in the *m*RCT and Current Controlled Trials are responsible for creating and maintaining this new database, which at November 2003 contained over 500 records.

Research Findings Electronic Register (ReFER)

Although not strictly a register of ongoing research, another relatively recent initiative is worth mentioning briefly at this point. ReFER, a freely available Department of Health database (http://www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm), provides access to the findings of completed projects from the NHS R&D programme and the Department of Health's Policy Research Programme to cover the period between completion and publication. Its aim is to provide what it calls 'prompt sight' findings of research studies on health and social care questions well before formal studies are available or the results appear as journal articles. Investigators are invited to submit a summary of their research findings (systematic reviews of primary studies in addition to primary research studies) on a standard electronic template to ensure consistency. ReFER was launched in June 2000 and by March 2004 contained 1078 records.

US-based trials registers

ClinicalTrials.gov

A means of letting patients know about medical research, but also a source for those seeking information on ongoing research, ClinicalTrials.gov (http://clinicalTrials.gov) is a service provided by the National Institutes of Health (NIH) and developed by the National Library of Medicine (NLM). The first version of the system became available in 2000 and concentrated on NIH-sponsored trials. Subsequent versions have contained information about trials sponsored by other federal agencies such as the Food and Drug Administration (FDA), other federal government components and by the private sector. It is possible to conduct a focused search of the site by disease, location, sponsor, treatment and so on, or to browse by condition or general type of disease (bacterial, behavioural, etc.) or by sponsor. All clinical study information submitted to ClinicalTrials.gov is reviewed by the NLM and the database is updated daily. In October 2003 the site reached a landmark by posting its 1000th study sponsored by the private sector. It describes itself as the 'world's largest source of clinical trial information' and lists approximately 8600 federally and privately sponsored trials worldwide. Although the NIH site

is linked to the *m*RCT, it is worth searching separately as there appears to be a time lag between records appearing on their site and access to them through the *m*RCT. Another related website is http://clinicalstudies.info.nih.gov, which is maintained by the Clinical Center at the NIH and lists only intramural studies done at the NIH. ClinicalTrials.gov itself is mandated only to cover trials relating to serious and life-threatening diseases, but a recent study has suggested that even in studies of cancer it is deficient and far from comprehensive.[20]

CenterWatch

CenterWatch is a well-established site (www.centerwatch.com) dating from 1994, which provides patients and clinicians with information about clinical research, listing clinical trials being conducted internationally. The site may be searched by a quick keyword search or under specific headings (trial listing, drugs in clinical research, newly approved drugs, industry profiles and research centre profiles), where a drop-down list of index terms is available for searching.

Recent criticism of the site has focused on the fact that much of the trial information is not directly accessible to the user and the lack of a unique identifier makes it difficult to differentiate between single trials and multisite trials.[62] A new section on the site, Centerwatch World, has been created specifically to list international trials. This lists international clinical trials according to medical topic and, although the listings are by no means exhaustive, there is also a list of useful links to international research centres.

Subject-specific trials registers

Cancer.gov site and PDQ cancer information database

The National Cancer Institute's Cancer.gov site in the USA contains a wide range of information about cancer and also clinical trials information provided through the PDQ cancer information database. PDQ is updated regularly and provides abstracts of ongoing treatment, supportive care, diagnostics, genetics, screening and prevention clinical trials in the USA and other countries, including all National Cancer Institute-funded clinical trials. The database also contains abstracts of clinical trial protocols. The extensive cancer clinical trials registry lists approximately 1600 active clinical trials at http://www.cancer.gov/search/clinical_trials and is available for patients, health professionals and the public. It includes information on understanding trials, deciding whether to participate in trials and finding specific trials listed in PDQ, plus research news and other resources.

UK register of clinical trials in cancer (UKCCCR)

The register of clinical trials in cancer is a database of all RCTs of cancer therapy whether Phase II or III, located at http://www.ctu.mrc.ac.uk/ukcccr/. The records from the UKCCCR are included on the *m*RCT, which receives a minimum core dataset and then links back to the original records in the UKCCCR.[66]

The International Cancer Research Portfolio (ICRP)

In September 2000, cancer research funders from the USA and the UK joined together in a partnership to classify their cancer research portfolios using a classification system called the Common Scientific Outline (CSO). On 26 June 2003, three members of the CSO (UK National Cancer Research Institute, US NCI and US Congressionally Directed Medical Research Programs) opened a new website which will provide a platform for the groups to share their portfolios with the wider community. Known as the International Cancer Research Portfolio (ICRP) and located at http://www.cancerportfolio.org, it allows users to search, browse and sort cancer research by type of cancer, area of research or funding organisation. Approximately 10% of research studies in the database have been classified as trials.

AIDSinfo (formerly ACTIS)

ACTIS was established in 1988 following the passing of legislation in the USA requiring registration of all clinical trials involving AIDS and HIV. In December 2002, ACTIS merged with its sister service, the HIV/AIDS Treatment Information Service (ATIS), forming AIDSinfo at http://www.aidsinfo.nih.gov to provide access to wide-ranging resources on HIV/AIDS research, treatment and prevention for health care providers and consumers together with a comprehensive database of government- and industry-sponsored HIV/AIDS clinical trials.

Because industry registration of all clinical trials involving HIV and AIDS has been mandatory since 1988, a much greater proportion of the trials listed in AIDSinfo are industry sponsored than is normally the case in the USA.[67]

PsiTri

This database of RCTs of mental health treatments is a joint project between the Cochrane Collaborative Review Groups within mental health, the EU-PSI editorial base at the University of

Helsinki and the National Library of Health Sciences at the University of Helsinki, which produce and maintain the database.[68] PsiTri contains bibliographic references on published trials but also information about the trials themselves. The registers contain results of searches from a vast range of data sources, unpublished and published, electronic and printed (at http://www.terkko.helsinki.fi/eu-psi/psitri.htm). The current status of each trial is given in a controlled vocabulary field in which options are completed, ongoing, planned or aborted. It is unclear how frequently this type of information is updated, although each record does have a date created and date modified field, which allows some check on currency.

Stroke Trials Directory (http://www.strokecenter.org/trials/)

The Stroke Trials Directory is a registry of clinical trials testing therapeutic interventions for stroke and cerebrovascular disease. Other features include a database of stroke interventions in clinical trials (drugs or procedures), lists of stroke scales and clinical assessment tools and an archive of stroke trial news reports. The registry information is open to all and free of charge. The website itself does not advertise or organise trials. The resource belongs to the Internet Stroke Center, a non-profit academic website of Washington University School of Medicine in St Louis and is a collaboration between Washington University, the American Stroke Association and the National Institute of Neurologic Disorders and Stroke (NINDS) at the NIH.

The directory provides links to Cochrane reviews when available and to ClinicalTrials.gov. The priority of the Stroke Trials Directory is stated as being "to list all ongoing and recently completed multicentre, randomised trials of therapeutic interventions for acute ischemic stroke or secondary stroke prevention", although trials of haemorrhagic stroke, intracerebral haemorrhage and stroke recovery have now also been added. The owners of the database acknowledge that as the project is relatively new and has only recently received funding support, "much of the information in the database is still preliminary or incomplete". To date there are approximately 500 records on the database, around one-quarter of which are ongoing.

Other sources

In addition to numerous trial registries, there are other areas of 'grey literature' which warrant searching for information about ongoing trials, in particular meeting abstracts and conference proceedings. Krzyzanowska and colleagues[69] attempted to determine the rate of full publication of large randomised trials presented at the annual meetings of the American Society of Clinical Oncology (ASCO) and discovered that, of a study sample of 510 abstracts from large Phase III randomised controlled trials presented at ASCO meetings between 1989 and 1998, a substantial number (26%) of trials referred to remained unpublished 5 years after the presentation.

An earlier systematic review[70] examining the subsequent full publication of biomedical results initially presented in abstract form reported a weighted mean rate of publication of 44.8% (95% CI 44.0 to 45.6).

This research and other guides such as that on the CRD website[71] suggest that an extensive search for ongoing trials should include any abstracts and conference proceedings relevant to the subject in hand. Another piece of work[72] revealed that a search of meeting abstracts in Science Citation Index and BIOSIS retrieved many RCTs that were not indexed in MEDLINE or EMBASE, as these databases do not index the journal supplements in which these meeting abstracts often appear. Given that as many as 50% of all trials initially presented in abstract form at meetings will not subsequently be published as full-length reports,[70] there is a real possibility of bias in a systematic review if these are not located.

Royle and Bidwell[72] concluded that despite misgivings over methodological detail contained in meeting abstracts and the standard of their peer review, they can nonetheless provide "useful early indication that a trial has been done (particularly in the case of a new or emerging technology)" and the authors can be contacted for further details. They recommend that a search for meeting abstract information should encompass Cochrane's CENTRAL database, the last 12 months of MEDLINE and EMBASE and a search of SCI and BIOSIS with the document type limited to meeting abstracts.

Dissertations are another 'grey source' of data on ongoing or completed but otherwise unpublished trials. Before expending too much time searching university catalogues and other sources, it is worth noting the results of a recent study[73] examining dissertations as a source of trials information. The conclusion here is that "searching for and retrieving unpublished dissertations involves considerable effort and appears to influence the conclusions of reviews only rarely". However, the

recommendation is that researchers preparing systematic reviews should "allocate time and resources to the identification, retrieval and analysis of dissertations" but also "be prepared for the eventuality that dissertations do not change the findings or conclusions of a review".

Science Citation Index

Access to the Science Citation Index is obtained through the Web of Knowledge, an integrated platform designed to support research in academic, corporate, government and not-for-profit organisations at www.mimas.ac.uk, using Athens authentication. SCI is a multidisciplinary index including approximately 362,000 new cited references per week.

BIOSIS

BIOSIS is a subscription-based service updated quarterly whose Biological Abstracts/RRM (Reports, Reviews, Meetings) service provides non-journal information from over 1500 meetings and conferences.

Biomed Central

Using Biomed Central, it is possible to gain free access to abstracts or proceedings of meetings which have appeared as supplements in the journals *Arthritis Care*, *Breast Cancer Research*, *Critical Care* and *Respiratory Research*. It is also possible to search meetings published in the Biomed Central meeting abstracts service (http://www.biomedcentral.com/meetings) by browsing published meetings or searching the complete meetings database by keyword search.

ISI Proceedings

ISI Web of Knowledge is an integrated platform designed to support research in academic, corporate, government and not-for-profit organisations at www.mimas.ac.uk. Accessed via an Athens password, it allows access to ISI Proceedings, which contains over 2.5 million records for more than 60,000 conferences for the years 1990–2002. It is updated weekly, amounting to the addition of some 225,000 records each year. The database can be searched by topic, author, source title, conference and address. Among the benefits of using ISI Proceedings is the ability to locate published findings on new research and to locate papers which have not been published in the journal literature but may give an indication of trials which are ongoing but have yet to be reported.

NLM Gateway

This web-based system (http://gateway.nlm.nih.gov/gw/) allows simultaneous searching of the NLM's numerous retrieval systems. The Gateway provides an interface to collections containing information which does not logically belong in PubMed, LOCATORPlus or other established NLM systems, such as meeting abstracts and conference proceedings, and therefore is a potential source of references to ongoing research. The Gateway also searches the HSRProj database (http://www.academyhealth.org/hsrproj/index.htm), which provides access to ongoing grants and contracts in health services research, including health technology assessment and the development and use of practice guidelines.

Medicalconferences.com

This searchable database (http://www.medicalconferences.com) provides free access to information on over 7000 medical conferences and other events and links to conference websites, enabling the user to access any references to new and ongoing research at an early stage. The simple search facility covers keyword, title and location.

Zetoc

This is the British Library's Electronic Table of Contents of around 20,000 current journals and 16,000 conference proceedings published each year. It covers the period from 1993 to the present and is updated daily. It is free to use for all JISC-sponsored UK higher and further education institutions and the NHS.

Specialist organisations

It may be worth searching abstracts of meetings issued by specialist organisations (these may be web-based or hard copy) within one's subject area. For example, it is possible to access abstracts such as the meetings of ASCO (http://www.asco.org). This provides access to a searchable archive of abstracts from ASCO's annual meetings between 1995 and the present.

Information on drugs in development

Pipeline sources versus publicly available trial registers

A recent study[20] compared two distinct types of data sources in order to find information on drugs for prostate or colon cancer: the trials registers available on the Internet and industry sources about drugs in development which are sometimes referred to as 'pipeline sources', in this case PhRMA Survey, What's in the Pipeline and the NDA Pipeline. The pipeline sources' coverage was more comprehensive than the publicly available registers in terms of listing specific drugs in Phase III trials.

A widely used pipeline source is Pharmaprojects, which describes itself as "the leading source of global business intelligence tracking drugs in R&D". This subscription-based service provides extensive product profiles for specific drugs including their state of development in any country (Phase I, II or III trial). Adis International R&D Insight, another fully searchable pipeline database providing tracking and evaluation of drugs, is an alternative to Pharmaprojects.

UK Medicines Information (UKMi)

This is an NHS pharmacy-based service available on the Internet at http://www.ukmi.nhs.uk. Within its new products section it is possible to search 'New Medicines on the Market' and access summaries prepared by regional medicines information units. The 'New Medicines in Clinical Development (Stage 3)' section of this site, which aims to provide comprehensive early intelligence evaluations of new and normally unlicensed drugs, is password protected for NHS staff only.

MEDLINEplus

Useful background to specific drugs may be found via this NLM site at www.nlm.nih.gov/medlineplus/druginformation. However, if one is seeking information about drugs in clinical research studies, ClinicalTrials.gov, one of the standard US-based registers mentioned previously should be used.

Food and Drug Administration (FDA)

The FDA (http://www.fda.gov/cder/) plays a role in encouraging submission of information on ongoing trials, providing guidance for the pharmaceutical industry on submitting protocol information to the ClinicalTrials.gov data bank.

The FDA requires that sponsors must submit information no later than 21 days after the trial is opened for enrolment. Supplemental information can be submitted at 30-day intervals. To ensure that the information available through the databank is timely and accurate, the FDA also encourages industry to review, verify and update all active protocol records on a semi-annual basis at the very least.

In addition to ensuring that such information is submitted to ClinicalTrials.gov, the FDA is itself a little-used source of trials information.[74] As part of the regulatory process of drug approval in the USA, sponsors must submit a New Drug Application to the FDA. These applications contain extensive information about the studies conducted to back up claims about the safety and efficacy of a drug. FDA officers review these data as part of the evaluation process. The original study material is not available to the public but the FDA reviews themselves are, and it is the usefulness of this unpublished trial information that MacLean and colleagues[74] examine.

In brief, the conclusions of the study are that not including unpublished FDA trial data is not likely to introduce bias as there appears to be little difference either methodologically or in terms of results between FDA and published data. The authors go on to suggest that data from FDA reviews should be considered a viable additional source of data for systematic reviews but only after being subject to the same methodological scrutiny as published data and only in reviews where there is a paucity of published data or where there is a reason to believe that FDA data may be systematically different from published data.

A review of the study in *The Lancet*,[75] although acknowledging the authors' overall conclusion that quality is similar between published and unpublished studies, nonetheless believes one of its most important messages is that the FDA is an important source of unpublished trials, questioning why so many of these FDA trials go unreported and advocating once more the need for prospective registration of RCTs. Similarly, a review in *Bandolier*[76] advocates that "pharmaceutical companies and others should be encouraged to make public that which is unpublished so that any doubt can be removed". Those who are interested in accessing this little-used source of trial information should go to the FDA website at http://www.fda.gov/cder/ and select the 'New and Generic Drug Approvals' section, which can then be searched through an A–Z index of drug name. Reviews that have been posted relating to a specific drug will be located here alongside approval date and any related correspondence.

Pharmaceutical industry – professional and commercial bodies

The position of pharmaceutical companies with regard to unpublished trial information has long been problematic. Pharmaceutical companies claim that clinical trial reports are 'commercially valuable intellectual property', but how much of this largely unpublished information should they make available to the public? Roberts and colleagues[77] report their unsuccessful attempts to obtain information on unpublished trials on the use of human albumin solution in the treatment of hypovolaemic shock during the preparation of a

Cochrane review. Neither the manufacturers nor the Medicines Control Agency proved helpful in this.

However, some initiatives to improve accessibility of industry-sponsored trials in the UK have been made by Schering Health Care, which in 1996 agreed to put information about all their ongoing trials on the Cochrane CENTRAL of Controlled Trials and GlaxoWellcome (now GlaxoSmithKline), which in 1998 announced that they would register all their clinical trials for new products worldwide and make this information available to health professionals.[78,79] Protocols for completed Phase II and III studies would be registered at the time of regulatory approval and would be updated at least annually with protocols from the company's large-scale Phase IIIb and IV studies. They have also committed themselves to assigning a unique identifier to each trial.

A user password is required to search the Glaxo database (http://ctr.glaxowellcome.co.uk/) and this is released only to researchers and healthcare professionals in order to avoid accusations of direct advertising to other parties. GlaxoSmithKline believe that their decision makes their products more credible and will increase public confidence that clinical decisions are based on reliable evidence.

The Association of the British Pharmaceutical Industry followed on these initiatives by advocating that from 2001, its members should register all their trials. On 6 May 2003 a new website was launched at https://www.cmrinteract.com/clintrial/ with details of clinical trials involving UK patients undertaken by pharmaceutical companies.[80] This is believed to be the first database of its kind launched by any representative body of the pharmaceutical industry. It describes itself as "a freely available and searchable register of retrospective phase III clinical trials and ongoing phase IV clinical trials in the UK". To September 2003 five firms had begun to contribute data (Novartis, Schering, Merck Sharpe and Dohme, Wyeth and Aventis) and it was hoped that Glaxo and others would also contribute in due course to the register, which at that date comprised 88 trials (personal communication). The CMR International database will be linked to the Current Controlled Trials Register.

Elsewhere, Chollar[67] describes the fear felt by US pharmaceutical companies of compromising their competitive advantage by agreeing to trial registration, but it is hoped that consumer pressure and the 1997 Food & Drug Administration Modernization Act legislation will ultimately force progress here also.

Other sources of information on drugs in development

Numerous other sources of pharmaceutical information are available (British National Formulary, Drug and Therapeutics Bulletin, eMIMS monthly, British Pharmacopoeia Online and TOXBASE), many on a subscription-only basis. However, information on ongoing trials is very limited in these and if access to pipeline sources is unavailable then trials registers such as *m*RCT or NRR will still be the best port of call. Patents databases are another source of information on drugs in development. An excellent site is the European Patent Office gateway Esp@cenet (http://ep.espacenet.com/search97cgi/s97_cgi.exe?Action=FormGen&Template=ep/EN/home.hts), which allows separate searching of British, European and worldwide patent resources. Because of the size of the databases, one needs to formulate a precise search for information using the advanced search facility, otherwise the amount of information retrieved will be unmanageable. The US Patent and Trademark Office site (http://www.uspto.gov/patft/) is another extensive resource in this area, offering quick and advanced searching. Again, one needs to have a precise idea of what one is looking for if the resource is to be a useful addition to one's search strategy.

Searching the Internet for ongoing trials

The Internet has facilitated access to numerous sources of information on ongoing trials, particularly web-based registries. It has been suggested, however, that there is still a need for broader searches using the Internet through search engines such as Google and Northern Light, which allow more sophisticated Boolean searching, in order to find what they describe as 'digital footsteps' of RCTs, which do not get into trials registers.[81] Examples of these would be mentions of trials contained in grant proposals or on the websites of funding agencies or individual research workers. Eysenbach and Wyatt's paper[81] provides an analysis of how individual search engines may be used and their levels of sophistication. Their proposal is to develop specialised search engines which would facilitate searching for ongoing trials. They could also contain expert knowledge on sites containing information on ongoing studies in addition to providing access to dynamic databases and meta-trial registers. Hence the Internet could be seen as playing an important role in linking

registers of clinical trials given the seeming acceptance that there is unlikely ever to be one central multinational database. In fact, some of the trials registers already fulfil part of what Eysenbach and Wyatt are recommending by providing a list of links to other registers through the Internet.

The usual concerns raised when obtaining information through the Internet will be encountered here – data retrieved through the web quickly become outdated, trials described as ongoing may be discovered to be completed and already published. There is also the concern over the quality of material appearing on the web and the fact that it has not been peer-reviewed. Further questions relate to the inability to formulate as precise a search strategy using the web as is possible using electronic databases, necessarily making such searches time consuming and therefore costly.[82,83]

Nonetheless, the web remains a useful tool in retrieving information on ongoing trials, whether used as Eysenbach and Wyatt suggest it may be in the future or as currently in providing access to web-based registries or providing cross-references and links between these.

A further assessment of six trial registers

We undertook an assessment of the characteristics of what the research team considered to be six of the main registers: *m*RCT, ISRCTN Register, NRR, Cancer.gov, ClinicalTrials.gov and Centerwatch.com between July and August 2003. The characteristics assessed cover information available in the registers, information retrieval, search and exporting facilities (see Appendix 6 for the evaluation form used and the completed forms for the six registers). The results are summarised in *Table 6*. Both information specialists extracted the data separately, results were compared and any disagreements were discussed and resolved.

Information available

In most registers, abstracts or summaries of trials were given. None of the registers provided direct access to protocols, although all gave the study location and principal investigator so that attempts could be made to obtain protocols through these sources. Cancer.gov gave two versions of the abstract, one for patients and the other for health professionals, the latter providing more comprehensive information.

All registers provided either free public access or registration. The GlaxoSmithKline register on the *m*RCT was available only to healthcare professionals, who are required to register separately.

With the exception of Centerwatch.com, whose purpose is to recruit potential study participants, all registers included both ongoing and closed trials. In Cancer.gov and ClinicalTrials.gov it was

TABLE 6 *Assessment of selected registers of ongoing trials*

	***m*RCT**	**ISRCTN Register**	**NRR**	**Cancer.gov**	**Clinicaltrials.gov**	**Centerwatch.com**
General information						
Sponsor/producer	Current Controlled Trials	Current Controlled Trials	Department of Health produced by Update Software	US NCI	US NIH, developed by US NLM	CenterWatch
Type of information available	Dependent on source of record	Abstracts	Abstracts	Abstracts[a]	Comprehensive summaries	Descriptions
Diseases/interventions included	All	All	All	Cancer	All	All
Multinational/national	Multinational	Multinational	National	Multinational	Multinational	Multinational
Accessibility	Free registration	Free public access	Free public access	Free public access	Free public access	Free public access
Completed/ongoing trials	Both	Both	Both	Both	Both	Ongoing
Proportion of ongoing trials	Unknown	Unknown	Unknown	Available	Unknown	Available
Total No. of records (Y/N)	Y	Y	Y	Y (estimate)	Y	Y (estimate)

continued

TABLE 6 *Assessment of selected registers of ongoing trials (cont'd)*

	***m*RCT**	**ISRCTN Register**	**NRR**	**Cancer.gov**	**Clinicaltrials.gov**	**Centerwatch.com**
Specific information on trials (Y/N)	(Mostly dependent on provider of record)			(Some data only in 'advanced search' form)		[b]
Study ID	Y	Y	Y	Y	Y	Y
ISRCTN	Y	Y	Y	N	N	N
Title	Y	Y	Y	Y	Y	N
Summary of purpose	Y	N	Y	Y	Y	Y
Recruitment status	Y	N	Y	Y	Y	Y
Study design	Y	Y	Y	Y	Y	N
Sample size	Y	N	Y	Y	Y	N
Participant eligibility	Y	Y	Y	Y	Y	Y
Study start/end date	Y	N	Y	N	Y	Y
Intervention(s)	Y	Y	Y	Y	Y	Y
Outcomes	Y	Y	Y	Y	Y	Y
Length of follow-up	Y	N	Y	Y	Y	Y
Study location	Y	Y	Y	Y	Y	Y
Principal investigator	Y	Y	Y	Y	Y	Y
Information retrieval General appearance and ease of navigation (poor, good, excellent)	Good[c]	Good	Good[d]	Excellent	Good	Good
Help feature (Y/N)	Y	Y	Y	Y[e]	Y	Y
Links to other sources(Y/N)	Y	Y	Y	Y	Y	Y
Search facilities	(Quick and advanced search facilities)	(Quick and advanced search facilities)		(Basic and advanced search facilities)[f]	(Basic, focused search and browse facility)	
Textwords (Y/N)	Y	Y	Y	N	Y	Y
Index terms (Y/N)	N	N	Y	Y	Y	Y
Phrases (Y/N)	Y	Y	Y	N	Y	Y
Boolean logic (Y/N)	Y	Y	Y	N	Y	Y
Truncation (Y/N)	Y	Y	Y	N	N	Y
Limits (Y/N)	N[g]	N	Y	N	Y	Y
Response time[h] (poor, good, excellent)	Good	Good	Good	Excellent	Good	Good
Frequency of updating (Y/N)	Y	N	Y[i]	N	Y	N
Exporting facilities						
Mark records (Y/N)	N	N	N	Y	Y	N
Download (Y/N)	N	N	N	Y	Y	Y
Email results (Y/N)	N	N	N	N	N	N

[a] Two versions of the abstract are available, one for patients and the other for health professionals.
[b] Only summary information is available, the object of which is to 'advertise' the study to potential participants. There are wide variations in the amount of information given.
[c] Inconsistency in requirement to enter registration details noted.
[d] The appearance of several registers and the need to display and browse records from each one separately can be cumbersome.
[e] Also gives on-line help.
[f] Must use search 'forms'.
[g] Can limit to selected registers.
[h] Observation at time of searching.
[i] NRR is updated quarterly; however, it is not clear how up-to-date the individual records are.

possible to select either option. The NRR has a separate listing of completed projects within each database.

Most registers provided most of the information which was regarded as being important, including objectives, design, sample size, participant eligibility, interventions, outcomes and length of follow-up (see *Table 6*). In order to access full information about trials in Cancer.gov it was necessary to select the advanced search form.

Information retrieval

Although a subjective judgement has been made, overall the general appearance of the registers and ease of navigation were considered to be good, with Cancer.gov standing out as being excellent. With reference to NRR, however, it was noted that the appearance of several registers and the need to display and browse records from each separately was considered cumbersome. There was also inconsistency within the *m*RCT for the requirement to enter registration details. In particular, on some occasions a password was required before any searching could take place, on others a search could be done but at the stage where documents could be accessed this was not possible without a password, then on others full access to the register was possible without a password.

All registers had a 'help' facility, with Cancer.gov having additional on-line support. This might include such things as searching, navigating the site, explanations of the contents of individual records and general background information about clinical trials.

Search facilities

There was variation in the level of sophistication of the search engines. With the exception of NRR and Centerwatch.com, a choice was offered between quick/basic or advanced searching. ClinicalTrials.com offered a 'browse' facility. Cancer.gov used search 'forms' where the user must select the type of cancer, type of trial or location of trial from drop-down menus. On the one hand this can be convenient but on the other could be regarded as restrictive by the information specialist because it is not possible to input textwords, phrases or search logic, as in the other registers.

*m*RCT allowed ordering of results by relevance, alphabetically by title or in order of the constituent registers. It also had a 'sounds like' feature that is useful when searching for terms which sound the same but are spelled differently, such as hemophilia and haemophilia. Clinical Trials.gov automatically added synonyms to searches.

In three registers (ISRCTN, Cancer.gov and Centerwatch.com), no information seemed to be available about how frequently they were updated. Although the NRR is updated quarterly, it is not clear how up-to-date the records contained in it are.

It was possible to print records in all registers using the web browser's print function. Cancer.gov and ClinicalTrials.gov allowed selected records to be marked then saved using the web browser's 'Save as' function. It was possible only to print pages in *m*RCT, ISRCTN and NRR. None of the registers allowed emailing of results.

Commentary

One challenge for information specialists and reviewers is ascertaining whether a study meets the inclusion criteria of the systematic review. In our evaluation, most registers provided enough information to be able to make an initial assessment of this.

A further challenge is, out of a number of studies retrieved, being able to differentiate between those which are unique references to a trial and those which are multi-entries for one study. Study IDs were given in all registers; however, this is not a reference which is universally unique to the study. The ISRCTN is a more reliable method of identifying a trial since this is a unique number. However, this was introduced in 2000 and is not yet widely adopted. In only three out of the six registers was it available. Even where data are given on participant eligibility, study design, interventions and outcomes, sorting references can still be difficult.

Searching trial registers: two case studies

Two cases

The information team at the West Midlands Health Technology Assessment Collaboration adopts a standard protocol for searching trials registers for identifying ongoing trials, which comprises searching the *m*RCT and NRR.

While undertaking a recent HTA report on the effectiveness of imatinib in treating gastrointestinal stromal tumours (GISTs), it was felt that a more comprehensive search for ongoing trials would be required. Imatinib is a new drug for the condition and scoping searches indicated

that there were many studies in progress. The search strategy was extended to include other trials registers. Several observations were made as follows:

- Additional studies were identified in registers included in the *m*RCT when searched separately.
- There was duplication of entries for the same trials within registers.
- It was difficult to identify the duplicate entries for the same trial
- A significant number of additional studies were identified by searching more extensively.

The searches were documented and the methods duplicated for searching for a more established cancer drug and the results compared. The second search was for the effectiveness of fludarabine for treating B cell chronic lymphocytic leukaemia (CLL), the topic of a technology assessment which was undertaken in 2002.

Methods

The search questions presented are:

- Case I: imatinib for the treatment of patients with unresectable and/or metastatic GISTs
- Case II: fludarabine as second-line therapy for B cell CLL.

The following registers were searched: *m*RCT, NRR Issue 3, 2003, ClinicalTrials.gov (NIH), ICRP, Current Trials (MRC Clinical Trials Unit), UKCCCR National Register of Cancer Trials, CancerBACUP and Cancer.gov (NCI).

Search terms for Case I: unless stated otherwise, the registers were searched using the drug terms Imatinib, Glivec, Gleevec, STI571, ST1571 and the results browsed for references to the relevant population.

Search terms for Case II: search terms were fludara (where truncation allowed), fludarabine. Where possible these were combined with terms for CLL. Otherwise the yield was browsed for relevant trials.

Searches were carried out in September and October 2003.

Results

The results of the searches are presented in *Tables 7*, *8* and *9*.

A significant number of additional trials were identified by searching NRR and ClinicalTrials.gov separately. Although these two registers are included in *m*RCT, the additional studies could not be identified from there. There may be several reasons for this but the most likely one would be that the mRCT had not been updated.

There was duplication of entries for the same trials within registers and this was especially apparent within the NRR. It is also extremely difficult to ascertain which entries might refer to the same trial.

If the standard protocol had been adopted for these searches, a significant number of trials would have been missed.

Extensiveness of literature searching

Much has been written about the effectiveness of extensive literature searching in overcoming the risk of publication bias in systematic reviews.[84–86]

TABLE 7 *Case study 1: results of searches of trials registers for imatinib for treating unresectable and/or metastatic GISTs*

	*m*RCT	NRR[a]	ClinicalTrials.gov[a]	ICRP	Current Trials[a]	UKCCR[a]	CancerBACUP	Cancer.gov
Records retrieved	7	41	67	13	0	0	1	5
Records selected	2	6	2	1	0	0	0	2
Duplicate records	1 (NRR)	3 (NRR)	1 (Cancer.gov and *m*RCT)	0	0	0	0	1 (*m*RCT and ClinicalTrials.gov
New records	1	3	1	1	0	0	0	1

[a] Currently being updated in *m*RCT.

TABLE 8 *Case study 2: Results of searches of trials registers for fludarabine for treating B cell CLL*

	*m*RCT	NRR[a]	ClinicalTrials.gov[a]	ICRP	Current Trials[a]	UKCCR[a]	CancerBACUP	Cancer.gov
Records retrieved	56	123	102	19	0	3	11	31
Records selected	24	112	12	4	0	1	5	13
Duplicate records	15 (7 *m*RCT; 3 ClinicalTrials.gov; 1 NRR and CancerBacup; 3 NRR)	95 (3*m*RCT; 1*m*RCT and CancerBacup; 91 NRR)	3 (*m*RCT)	1	0	1 (NRR)	3 (CancerBacup)	1 (NRR)
New records	9	17	9	3	0	0	2	12

[a] Currently being updated in *m*RCT.

TABLE 9 *Yield of ongoing trials – standard protocol versus extended strategy*

	Yield of ongoing trials using current standard (*m*RCT + NRR)	Yield of ongoing trials using structured strategy	Captured additional ongoing trials
Case study 1: imatinib	4	7	3
Case study 2: fludarabine	27	53	26

One piece of research on extended search methods for identifying RCTs for systematic reviews concluded that searching beyond major databases such as MEDLINE and EMBASE identified many additional RCTs and of all the sources searched "specialist databases and trial registries were the most effective".[85] It does not state, however, whether these trials are published or unpublished. Indeed, little has been written on the impact of information from ongoing trials on existing evidence and more specifically about the best methods of searching for this type of information.

A recent study of search strategies for locating trials for inclusion in Cochrane reviews is due for publication shortly.[87] The overall aim of this study was to analyse sources searched in Cochrane reviews, determine the proportion of trials included in the reviews that are indexed in major databases and compare the quality of these trials with those from other sources. Within the work, however, there is useful data on unpublished and ongoing trials and how to search for this type of information. An analysis of the publication status of the trials located by what the authors describe as non-core databases (i.e. other than CENTRAL, MEDLINE and EMBASE) revealed that 37% were classified as unpublished, 48% as published and 16% as a combination of the two. Of the larger trials (i.e. those above a median of 74 patients) located in this manner, 25% were found in meeting abstracts, 25% were in complementary medicine journals, 16% were drug company reports, 16% were manuscripts in publication, 6% were ongoing trials and 12% were found using various other means.

The authors found no evidence that trials located outside the core databases had poorer allocation concealment or smaller patient numbers than those found using the core databases. "The vast majority of higher quality non-CME (core database) trials were either unpublished (drug company reports, abstracts, unpublished manuscripts) or published in complementary medicine journals." This study found that the average size of the unpublished trials was larger than published trials. As larger trials have greater impact than smaller trials on overall estimates of treatment effects in meta-analysis, it seems important that these larger trials should not be missed. This study[87] does not go on to look at whether excluding those trials which were found by searching non-core sources would have made a difference to the results of the review, as it is not known whether the size and direction of treatment effects are systematically different in core compared with non-core trials. Nonetheless, the message from the study is that the most likely sources of trials not covered by the three main

core databases are not databases but unpublished sources (drug company reports, manuscripts in press or preparation or ongoing trials) or sources that are only indexed to a very limited extent (e.g. meeting abstracts or relevant foreign language journals). This leads the authors to offer useful advice on searching for unpublished (including ongoing) trials. They suggest handsearching meeting abstracts, contacting experts and manufacturers of drugs and looking at relevant journals in languages other than English to ensure a comprehensive search.

Formulating search strategies for locating ongoing trials

What conclusions can we draw as to the optimum strategy for locating ongoing trials? According to this review and assessment of sources of ongoing trials, our experiences from two case studies and given the law of diminishing returns plus the need in the real world to trade timeliness against exhaustiveness, we suggest the following strategy:

- **Step I:** Trials registers – national and international registers. If search time is limited we suggest the *m*RCT alone (as this encompasses other registers such as ClinicalTrials.gov), but bear in mind its limitations as discussed earlier.
- **Step II:** Trials registers – other subject-specific sites.
- **Step III:** Pharmaceutical sources – drug company websites and personal contacts, pipeline sources if accessible, FDA site.
- **Step IV:** Handsearching – abstracts, journals in languages other than English.
- **Step V:** Internet searching – following Eysenbach and Wyatt's suggestions.[81]

The review team must decide how far down the list they need to work, according to both the subject area and the requirements of timeliness and exhaustiveness for each particular review. We would suggest that steps I and II are essential, step III advisable and steps IV and V optional. Some pitfalls and points of interest to bear in mind when searching are highlighted in the previous two sections of this chapter, in which practical problems arising from actual searches for information on trials in progress during the preparation of HTA reports are highlighted. Resources may change within a very short space of time owing to a variety of circumstances and what was initially a useful tool may be devalued if, for example, some of its contributors no longer continue to update their entries or cease to send material at all, as is the case with the *m*RCT. Information specialists in particular should endeavour to keep up-to-date with developments in trial registers, which are a fast-moving area of information.

Chapter 5

Methods for assessing the impact of ongoing trials

The impact of ongoing trials may be assessed in an unstructured and informal manner in health technology assessment reviews (see Chapter 3). In this chapter, we aim to summarise and evaluate available methods that can be used for more structured and formal assessment. After a description of types of possible impact of ongoing trials, we outline major approaches to assessing ongoing trials. Methods for both descriptive and quantitative assessment are discussed. A case study is used to illustrate the application of different methods.

Possible impact of ongoing trials

Decisions made based on existing trials may or may not be altered when the results from ongoing (or unpublished) trials become available. For example, the results of ongoing trials may:

- answer research questions that have not been considered in previous trials (for example, different populations, different settings/ intervention strategies, and different outcomes)
- if the research questions are the same or similar, improve the precision and generalisability of estimates of effectiveness and cost-effectiveness
- overturn conclusions so that, for example, a positive result becomes negative.

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 5*). Although the existing evidence may be sufficient to answer some questions, it is unlikely that the evidence required to make decisions will be perfectly matched by the existing evidence. There may be no research evidence at all, or the existing evidence may not be relevant. Often, the existing evidence may be unconvincing because of methodological weaknesses or lack of statistical power. In almost all circumstances, lack of sufficient research evidence may be inevitable, although the nature and extent of evidence shortage may be different.

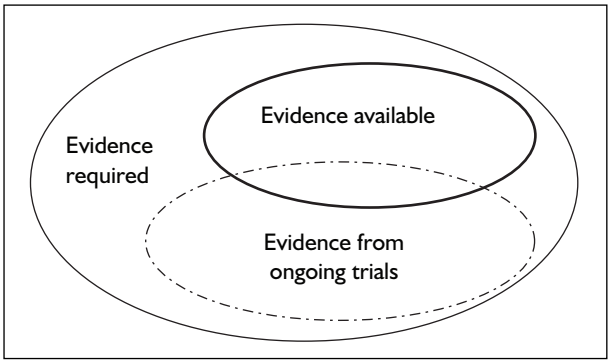

FIGURE 5 *Evidence required, already available and possible from ongoing trials*

In addition, either the need for evidence or the availability of evidence may change over time. Research evidence will accumulate by incorporating findings from newly completed research. To assess the impact of ongoing trials is to attempt to predict possible changes in estimates of treatment effect, based on information about ongoing trials and the existing evidence. If the available evidence comes 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 negligible or insignificant. If the scale of ongoing trials is substantial, ongoing trials may yield data that could overturn the estimates of effect 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 and quality of ongoing trials. The quantity of trials could be measured by using the number of trials and the number of patients or events. According to the quantity of ongoing trials, the robustness of the estimate of effects based on available trials may be tested by sensitivity analyses. For example, if a treatment effect based on available trials is positive but small or moderate, it could disappear owing to more negative results from ongoing trials. On the other hand, a large effect based on many completed trials is less likely to disappear by including negative results from ongoing trials.

Some authors have suggested methods to assess the need for further trials or to assess whether ongoing trials should be terminated.[21,22] These methods can be adopted for assessing the possible impact of ongoing trials. The purposes may be

different but the methodological questions are similar. A conclusion that there is no need for further trials or no need to continue ongoing trials is equivalent to a conclusion that the anticipated impact of future trials and ongoing trials is insignificant.

Characteristics of ongoing trials

Data about ongoing trials can be gathered from registers of clinical trials and conference proceedings (see Chapter 4 for sources of information about ongoing trials). Conference abstracts about ongoing trials may contain only limited information about trial design features but may provide preliminary results and early findings. The full trial protocol provides the most comprehensive information about trial objectives, design, inclusion/exclusion criteria, sample size, interventions compared, outcomes measured and length of follow-up. We may presume that a trial will be carried out precisely according to the trial protocol. However, it is common that a trial protocol may be changed, for example, because of the problem of patient recruitment, unexpected events or new evidence from other studies.[4] By comparing a sample of trial protocols and subsequent publications, Chan and Altman found that about 50% of trials changed, introduced or omitted at least one primary outcome and 10% of trials had major alternation to specified outcome analyses.[88]

Qualitative assessment of ongoing trials involves comparing major features of completed trials with those of ongoing trials (*Table 10*). It provides qualitative information about the possible impact of ongoing trials in terms of relevance, validity reliability and generalisability. This will be useful for addressing questions about whether the research questions are the same or similar in completed and ongoing trials.

Trial objectives

Depending on the developmental stages of a health technology, the objectives of trials in progress may be similar to or different from completed trials. The objectives of a trial can be characterised by three main dimensions: participants (patients), interventions (including comparators) and outcome measures. Other relevant issues include settings, those delivering interventions and length of follow-up.

The inclusion and exclusion criteria in ongoing trials are often different from those in completed trials. For example, early drug trials may mainly include patients with advanced disease or who have failed to respond to conventional therapies, whereas late trials may include patients with less severe diseases or newly diagnosed. If the ongoing trials do not include patients belonging to the population specified in a technology assessment review, such ongoing trials may be considered irrelevant.

The interventions evaluated in the ongoing trials need to be compared with those in the completed trials. Dose, frequency and period of treatment may vary. Comparators used in ongoing trials may be different from those used in completed trials. If a new drug has not been compared in trials with the current standard treatment or placebo, decisions will have to be made based on indirect comparisons using data from case series or cohort studies. It is well known that such indirect comparisons may yield biased inferences about the relative efficacy of health interventions.[89,90] The potential impact of findings from any comparative trials in progress will be crucial in cases where there is no existing evidence from controlled studies.

Early-phase trials often use surrogate outcomes or intermediate endpoints, whereas late-phase trials tend to use more clinically relevant outcomes. The

TABLE 10 *Comparison of features of completed trials versus ongoing trials*

Features	Completed trials	Ongoing trials
Number of trials		
Number of patients (and events)		
Phase and design		
Objectives		
Patients/settings		
Intervention and comparators		
Outcomes measured		
Length of follow-up		
Findings/results		

outcome measures used in ongoing trials need to be compared with those used in completed trials. Surrogate outcome measures may not be a good proxy for clinically relevant outcomes that are important to patients.[91] In addition, ongoing trials may measure longer term outcomes than completed trials. Quality of life is an important outcome which is only occasionally measured in clinical trials.

Design quality and information size

The quality of published trials is usually assessed based on reported information (e.g. journal articles), and it is often the case that details about trial design and methods are inadequately reported.[92] The assessment of the quality of ongoing trials may be more problematic owing to only limited information being available. The full trial protocol is the best possible document for this purpose. The important design quality items are method of patient allocation, allocation concealment, blinding of patients, those delivering intervention and people who measure the outcomes and how to deal with dropouts.[93] If the quality of ongoing trials is better than that of completed trials, the potential impact of ongoing trials will be considerable.

The information size of ongoing trials can be measured according to the number of ongoing trials and/or number of patients or events in ongoing trials. The information size (or weight) of ongoing trials versus completed trials will determine the relative importance of results of ongoing trials. The precision of estimated magnitude of treatment effect will depend on the sample sizes and event rates. If the existing evidence is small relative to ongoing trials, the possible impact of ongoing trials will be great, as will be further illustrated by some quantitative assessment methods below.

Quantitative methods

Quantitative data available from ongoing trials is often very limited. We may know the number of ongoing trials and the number of participants that the ongoing trials plan to include. Occasionally, preliminary results may be available, for example, from conference abstracts. For assessing the impact of ongoing trials, the information about them is used in combination with results of completed trials by some quantitative methods (for example, sequential monitoring boundaries and Bayesian predictive probability). In this chapter, we also consider some methods that assess purely the strength of the existing evidence without directly involving data from ongoing trials (for example, fail-safe N).

Cumulative meta-analysis

Defined as the repeated performance of an updated meta-analysis every time a new trial appears, cumulative meta-analysis is inherently Bayesian.[94] Cumulative meta-analysis could be retrospectively or prospectively carried out. It can be used to investigate changes in the results when new evidence is added and to determine as early as possible when a new treatment is convincingly effective or harmful. In cumulative meta-analysis, trials can also be ordered according to, for example, the event rate in the control group, the sample size and the study quality score. A further extension of cumulative meta-analysis is **recursive** cumulative meta-analysis that shows the evolution of estimated treatment effect over time by considering not only new evidence from new trials, but also updated data from old trials or retrieval of unpublished ones.[95]

Cumulative meta-analysis and related methods may also be useful to decide whether new trials are required and to monitor trials in progress.[96] In particular, chronological cumulative meta-analysis done retrospectively may show the trajectories of treatment effect over time and identify factors that predict changes in the magnitude of the treatment effect as new pieces of evidence are gathered.[97]

The treatment effect estimated in meta-analysis may change when new evidence is added because of the chance error, genuine heterogeneity (in terms of patients and interventions) or biases (including publication and related biases). Ioannidis and Lau[97] used cumulative meta-analysis to evaluate the evolution of estimated treatment effects over time for 60 interventions in two medical fields (pregnancy/perinatal medicine and interventions for myocardial infarction). They found that, with 500 accumulated patients, the pooled odds ratio may change by 0.6–1.7-fold in the immediate future. With 2000 patients included, the figures are 0.74–1.35-fold for pregnancy/perinatal medicine and 0.83–1.21-fold for myocardial infarction trials. It was suggested that "early wide oscillations in the evolution of the treatment effect for specific interventions may sometimes signal further major changes in the future".[97]

In cumulative meta-analysis, the magnitude of changes in treatment effect over time is usually graphically examined. However, the relative change in the treatment effect between

information steps can be more objectively measured by using the ratio of the estimated effect (e.g. the pooled odds ratio) at the next information step to the estimated effect at the current information step.[97] In addition, Mullen and colleagues[98] introduced concepts of sufficiency and stability for the application of cumulative meta-analysis. Sufficiency refers to whether additional studies are needed to establish the existence of the phenomenon, whereas stability is about whether additional studies will change the aggregate picture of the phenomenon. They also suggested indicators of sufficiency (the fail-safe ratio) and stability (the cumulative slope) in cumulative meta-analysis.[98] In this report, we focus on the method of sequential monitoring boundaries and stochastic curtailment, as suggested by Pogue and Yusuf.[99]

Optimal information size (OIS) and sequential monitoring boundaries

One problem of performing cumulative meta-analysis is inflated Type I error (α) due to multiple statistical testing. The overall sample size required for convincing evidence in a cumulative meta-analysis is not usually predefined. To deal with these limitations, Pogue and Yusuf[99] introduced the concept of optimal information size (OIS) and proposed the use of sequential monitoring boundaries for cumulative meta-analysis.

The sample size required in a single trial can be predefined according to presumed effect size, baseline event rate and acceptable level of Type I and II error. Similarly, the OIS is predefined for cumulative meta-analysis, by assuming realistic event rates and the minimal effect that is considered clinically worthwhile and biologically plausible.[99] For trials with binary outcome measures, the OIS can be calculated using

$$\text{OIS} = 2 \times \frac{(Z_\alpha + Z_\beta)^2 \times 2 \times P^* \times (1 - P^*)}{(P_C - P_E)^2}$$

where P_C is the event rate in the control group, P_E is the event rate in the treatment group and $P^* = (P_C + P_E)/2$. The estimated OIS is then used as a reference point for monitoring the results of cumulative meta-analysis utilising sequential monitoring boundaries or stochastic curtailment.

For example, Pogue and Yusuf[99] assumed that myocardial infarction patients admitted to the cardiac care unit would have a death rate of 10% after 1 year of follow-up. Based on their previous experience, even truly effective treatments generally reduce the risk of death by only 10, 15 or at best 20%. Suppose that a 15% reduction in mortality is considered worthwhile and that the rate of Type I and II error is $\alpha = 0.01$ and $(1 - \beta) = 0.9$, respectively, about 22,000 patients are required for cumulative meta-analysis.

It may be difficult to decide the possible 'true' treatment effect and estimated OIS is rather tentative in many cases. For assessing the possible impact of ongoing trials, the sample size of all completed trials and that of ongoing trials may be combined to obtain a **cumulative information size** (CIS). The estimated CIS may be used as the reference point to consider the certainty of results from completed studies. If the CIS is smaller than the OIS, we may conclude that the statistical power is still insufficient even when the ongoing trials are completed.

There are different statistical methods for monitoring the interim results of clinical trials. The Lan–DeMets α-spending function method is a flexible approach to constructing discrete sequential boundaries based on the choice of a function, $\alpha^*(t)$, which characterises the rate at which the error level α is spent.[100] The index t $(0 \le t \le 1)$ is the information fraction or the proportion of the total information. For example, let i_j be the information available at the jth analysis and I be the total information, $t_j = i_j/I$. For cumulative meta-analysis, i_j is the total number of patients after jth trial is added and I is the OIS. The Lan–DeMets OBF α-spending function is

$$\alpha^*(t) = \begin{cases} 0 & \text{when } t = 0 \\ 2[1 - \Phi(Z_{\alpha/2}/\sqrt{t})] & \text{when } 0 < t \le 1 \end{cases}$$

Numerical integration is required to use this method, but the calculation can be carried out using a computer program that can be downloaded from a website: http://www.biostat.wisc.edu/landemets/ (access date 15 July 2003; the document and program were provided by Reboussin, DeMets, Kim and Lan at the University of Wisconsin, Madison, WI, USA).

Stochastic curtailment method

Pogue and Yusuf[99] also explored stochastic curtailment[101] for predicting what the outcome will be when total information is collected. Assume that a statistic S_T will be used to test a null hypothesis H_0 when total information (T) is available, and a rejection region R has been decided so that

$$P\{S_T \text{ exist in } R | H_0\} = \alpha$$

and

$$P\{S_T \text{ exist in } \bar{R} \mid H_a\} = \beta$$

where $\bar{R}$ is the 'acceptance' region for H_0.

Assume that Dt is the available data at a point t before all information is available. For a positive trend, we may estimate the probability of rejecting the null hypothesis (H_0) when total information is reached, conditioned on the current data (Dt):

$$P\{S_T \text{ exist in } R \mid Dt, H_0\} = \gamma_0$$

If γ_0 is suitably large, people might reject H_0 at the point t before total information is collected. Similarly, for a negative trend, we can estimate the probability of failing to reject H_0 when total information is reached:

$$P\{S_T \text{ exist in } \bar{R} \mid Dt, H_0\} = \gamma_1$$

The calculation can be conducted according to methods suggested by Lan and Wittes.[102] The index t ($0 \le t \le 1$, the proportion of the total information) and cumulative Z-values (Zt) are calculated in the same way as for sequential monitoring boundaries. For estimating the probability of rejecting the H_0 when total information is reached, given the current data and assuming that H_0 is true, we can use the following equation:

$$Cp(0) = 1 - \Phi\left\{\frac{Z\alpha - Zt \times \sqrt{t}}{\sqrt{1-t}}\right\}$$

where $Z\alpha$ equals 1.96 or 2.58 depending on the Type I error rate. For a negative trend, the probability of failing to reject H_0 when total information is reached can be estimated by using

$$Cp(1) = 1 - \Phi\left\{\frac{Z\alpha - Zt \times \sqrt{t} \,/\, t}{\sqrt{1-t}}\right\}$$

To illustrate the Lan–DeMets method and stochastic curtailment method, Pogue and Yusuf[99] used an example of cumulative meta-analysis of 11 trials of intravenous magnesium for suspected myocardial infarction. They found that the cumulative Z-value was >1.96 ($p < 0.05$) or >2.58 ($p < 0.01$) after second or third trials were added, respectively. However, the monitoring boundary was not crossed until the 14th trial was included (cumulative Z-value 4.45 versus bounds 4.12) and the cumulative Z-value dropped to near zero when the last (also the largest) trial (ISIS-4) was added. Using the stochastic curtailment method, they found that the conditional probability to reject H_0 was <60%. They concluded that "the use of these monitoring techniques indicates that there was no conclusive evidence of the benefit of magnesium at any time".

Fail-safe N

Rosenthal[103] suggested a file-drawer or fail-safe N method to estimate the number of possible unpublished studies in a meta-analysis. This method may be useful for assessing the impact of ongoing trials according to the stability or robustness of positive findings from completed trials. It is a statistical method to estimate the number of unpublished studies required, with zero treatment effect on average, to overturn the statistically significant result in a meta-analysis. If the number of unpublished studies required to overturn the statistically significant result is large and therefore unlikely to exist, the impact of unpublished (or ongoing) studies is negligible. The fail-safe N (FSN) is calculated by,

$$\text{FSN} = \frac{k \times (Z_c)^2}{(Z_{\alpha/2})^2} - k$$

where k is the number of studies in meta-analysis, Z_c is the overall Z-value from the meta-analysis and $Z_{\alpha/2}$ equals 1.96 when $\alpha = 0.05$. The estimated fail-safe N needs to be considered in proportion to the number of published studies. Rosenthal[103] suggested that the fail-safe N may be considered as being unlikely if it is greater than a tolerance level of $X = (5k + 10)$. Recently, Mullen and colleagues[98] recommended a fail-safe ratio FSN/X as an indicator of sufficiency in cumulative meta-analysis. Here, sufficiency is about whether additional studies are needed to establish the existence of the phenomenon. However, the criterion of $5k + 10$ was not based on the objective evidence and its use may be controversial.[104]

The fail-safe N method is simple and easy to use, but may be criticised for overemphasising the importance of statistical significance. The average effect from unpublished or ongoing trials may not be zero, and the sample sizes of unpublished or ongoing trials may be different from published trials. It is not clear about how large a fail-safe N should be when the potential impact of unpublished or ongoing trials could be disregarded.

Bayesian data monitoring

Bayesian approaches provide a formal framework for estimating the probability distribution of a parameter of interest and synthesising evidence from multiple sources.[9,105] First, existing objective

evidence or subjective judgement is used to estimate a prior distribution about the parameter's value. Any new data are expressed by a likelihood function, which provides the probability of observing the actual data for any particular values of parameters. Then, Bayes' theorem is used to obtain a posterior distribution by integrating the prior distribution and the new evidence. The posterior distribution reflects the new beliefs about the parameter's value. The Bayesian methods are very useful for monitoring, analysing and interpreting data from clinical trials.[105] For assessing the possible impact of ongoing trials, we first discuss the method of Bayesian data monitoring in clinical trials[106] and then Bayesian predictive probability.[9]

The interpretation of results from interim analyses (or from completed trials) may be different for people who have different prior beliefs. To prevent overenthusiastic acceptance of a positive effect that might be observed by chance at the time of an interim analysis, Fayers and colleagues[106] suggested that the sceptical prior should be adopted.

Following Fayers and colleagues,[106] we use $\log(h_d)$ to indicate the observed treatment effect (log hazard ratio) and N_d to indicate the number of events from clinical trials. That is, the observed treatment effect is assumed to be normally distributed with a mean of $\log(h_d)$ and a variance of $4/N_d$:

$$\text{data} \sim N[\log(h_d), 4/N_d]$$

The observed data need to be considered with a chosen prior distribution. Sceptical prior assumes that the best guess of the unknown treatment effect is zero, but there is a small possibility (γ) that it is as large as or greater than a value of the alternative hypothesis [$\log(h_1)$]. Assuming that $\gamma = 5\%$ and with a chosen $\log(h_1)$, the square root of the variance for the sceptical prior distribution is

$$\sigma_{scep} = \frac{\log(h_1)}{1.64465}$$

We can estimate approximately the number of events that corresponds to the sceptical prior using the following equation:

$$N_p = \frac{4}{\sigma_{scep}^2}$$

Approximately, the sceptical prior $\sim N[0, 4/N_p]$. This is a normal distribution with a zero mean and a variance of $4/N_p$.

Based on the observed data and the defined sceptical prior, the posterior distribution is calculated by

$$\text{posterior distribution} \sim N\left[\frac{N_d \times \log(h_d)}{(N_d + N_p)}, \frac{4}{(N_d + N_p)}\right]$$

The estimated posterior distribution can be used to calculate the probabilities of the treatment effect being greater than any suggested values (as will be shown in the case study below). This method does not directly use data from ongoing trials.

Bayesian interim predictions

Considering data from completed studies as data from interim analyses, Bayesian approaches can be used to predict the chance of obtaining a 'significant' result when data from ongoing trials becomes available.[9] With a full Bayesian approach (prior used in predictions and analysis), the predictive probability that the future posterior tail area $P_{m+n}(\delta)$ will be less than ε is

$$P_m\{P_{m+n}(\delta) < \varepsilon\} = \Phi\left\{Z_m(\delta_1)\sqrt{\frac{n_0 + m + n}{n}} + z_\varepsilon\sqrt{\frac{n_0 + m}{n}}\right\}$$

where $\Phi(z)$ is the cumulative normal probability [for example, $\Phi(1.6445)=0.95$)], n and m are the number of events in the ongoing and completed trial, respectively, n_0 is the number of events for the prior distribution and δ_I is the value that the final interval will exclude (it may be zero for any benefit, or a value for 'the minimal clinically worthwhile benefit'). z_ε will be equal to 1.95 at the 5% level of statistical significance and 2.58 at the 1% level. In addition,

$$z_m(\delta_I) = \left(\frac{n_0\delta_0 + mX_m}{n_0 + m} - \delta_I\right)\frac{\sqrt{n_0 + m}}{\sigma}$$

where δ_0 is the prior mean and σ is the standard deviation (in survival analysis with proportional hazards, and δ is the log-hazard ratio, $\sigma^2 = 4$).

Spiegelhalter and colleagues also described a mixed approach in which prior is used for predictions but not in analysis.[9]

A case study – gemcitabine for pancreatic cancer

HTAR objectives and available evidence

In an HTAR, Ward and colleagues[107] evaluated the clinical and cost-effectiveness of gemcitabine as

first- and second-line therapy for pancreatic cancer. Newly diagnosed pancreatic cancers are often already at an advanced stage and many patients die within a few months of diagnosis. In addition to palliative care, the standard chemotherapy used for pancreatic cancer is 5-fluorouracil (5-FU), which may slightly improve survival and quality of life. Gemcitabine is a relatively new drug that inhibits DNA synthesis, and may be useful in the treatment of some solid tumours. It is indicated for the treatment of patients with advanced or metastatic adenocarcinoma of the pancreas or patients with 5-FU-refractory pancreatic cancer. For the first-line therapy, the key step is to compare gemcitabine and 5-FU for patients with advanced pancreatic cancer.

Reviewers of this HTAR identified many gemcitabine RCTs that were completed or still ongoing (*Table 11*). Only one fully published RCT compared 5-FU and gemcitabine as a single agent therapy, by Burris and colleagues in 1997,[108] which was considered to be the best evidence available and provided data on patients' survival outcome for the economic evaluation. In the Burris trial, 126 patients with locally advanced or metastatic pancreatic cancer were randomly allocated to the gemcitabine or 5-FU group. At 12 months, the survival rates were 18% and 2% for gemcitabine- and 5-FU-treated patients, respectively. The median survival was 5.65 months in the gemcitabine group and 4.41 months in the 5-FU group ($p = 0.0025$). According to additional data from industry (reported in the HTAR), the mean survival was 6.79 months in the gemcitabine group and 4.52 months in the 5-FU group. All patients in the trial died within 19 months.

Although the results of this single RCT suggested that gemcitabine may be more efficacious than 5-FU, HTAR reviewers commented that it failed adequately to prove the superiority of gemcitabine. First, a bolus infusion of 5-FU used in the trial may not be a valid control against which to evaluate gemcitabine, since such a method of administration is suboptimal for other gastrointestinal cancers. Second, more clinically active regimens of 5-FU used in other trials had shown similar survival rates to that by gemcitabine in the Burris trial. Furthermore, the trial had a low Jadad quality score (2/5), and included a small number of patients ($n = 126$).[107]

Relevant ongoing trials

Reviewers of this HTAR identified 12 RCTs from which the survival results were not yet available (*Table 11*). These ongoing trials evaluated gemcitabine alone or in combination with other agents as adjuvant, first-line or secondary therapy. There were no ongoing trials that had exactly the same objectives as the Burris trial, although there were a few that may be similar to the Burris trial. An ongoing trial (Trial 9 in *Table 11*) compared gemcitabine and 5-FU in patients with resected pancreatic cancer and who also received chemoradiation therapy. In two trials (Trials 2 and 8), gemcitabine was compared with 5-FU plus folinic acid (FA) in patients with unresectable or sectable pancreatic cancer. Although the control interventions or patients in these three ongoing trials were not exactly the same as that in the Burris trial, the results of these ongoing RCTs when available will provide additional evidence on the comparison of gemcitabine and 5-FU for the treatment of pancreatic cancer. The potential impacts of these three ongoing RCTs will be assessed in this case study.

Quantitative assessment

Cumulative meta-analysis related methods

The true relative efficacy of gemcitabine versus 5-FU is unknown. Because it is difficult to estimate the OIS, we used the CIS, that is, the total number of patients in the Burris trial and the three ongoing trials (CIS = 1186). The Burris trial reported a p-value of 0.0025, which is approximately equivalent to a z score of 2.81. The number of patients in the Burris trial ($n = 126$) was only about 11% of the total information. Using the Lan–DeMets α-spending function method, the estimated boundary ($z_b = 6.79$) is much greater than the observed z value ($z_o = 2.81$). Hence the statistical significant result observed in the Burris trial was not conclusive.

Using the stochastic curtailment method, the probability of rejecting the null hypothesis at the 5% level when total information is reached can be calculated as

$$\begin{aligned} CP(0) &= 1 - \Phi\left(\frac{Z\alpha - Zt \times \sqrt{t}}{\sqrt{1-t}}\right) \\ &= 1 - \Phi\left(\frac{1.96 - 2.81 \times \sqrt{0.11}}{\sqrt{1-0.11}}\right) \\ &= 1 - \Phi(1.09) = 0.14 \end{aligned}$$

With the current positive trend and assuming that the null hypothesis is true, the conditional probability of rejecting the null hypothesis when all information becomes available is only 14%.

Fail-safe N method

The fail-safe N is the number of additional studies (unpublished or ongoing) required to overturn the

TABLE 11 *Features of completed RCTs versus ongoing RCTs: gemcitabine for pancreatic cancer*

Trial	Interventions	Participants	Completeness
1. Burris *et al.*[108]	Gemcitabine 5-FU	126 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	Completed
2. Cantore *et al.*	Gemcitabine 5-FU + FA 5-FU + FA + epirubicin + carboplatin	106 patients with unresectable pancreatic cancer	Ongoing (Abstract, results not yet reported)
3. Moore *et al.*	Gemcitabine BAY12-9566	277 patients with pancreatic cancer	Abstract reported results
4. Rosemurgy *et al.*	Gemcitabine Marimistat (5 mg/day) Marimistat (10 mg/day) Marimistat (25 mg/day)	414 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	Abstract reported results
5. British Biotech	Gemcitabine + placebo Gemcitabine + marimistat	239 patients with pathologically confirmed pancreatic cancer	Press release only, reported results
6. Lygidakis *et al.* (1)	Curative or palliative surgery alone Curative or palliative surgery + gemcitabine + carboplatin + mitoxantrone + immunotherapy	512 patients with pancreatic cancer	Completed
7. Lygidakis *et al.* (2)	Surgery + gemcitabine + lipiodol + urografin with docetaxel + carboplatin + proluekin Surgery alone	26 patients with histologically confirmed resectable pancreatic cancer	Completed
8. European study of pancreatic cancer	Surgery + 5-FU/FA Surgery + gemcitabine Surgery alone	990 operable pancreatic cancer (adjuvant therapy)	Open No results
9. Trial of adjuvant fluroracil chemoradiation	Chemoradiation + 5-FU Chemoradiation + gemcitabine	330 patients with resected pancreatic adenocarcinoma	Open No results
10. Trial of gemcitabine with or without 5-FU	Gemcitabine Gemcitabine + 5-FU	320 patients with advanced pancreatic cancer	Closed No results
11. Trial of weekly i.v. P30 protein + tamoxifen vs i.v. gemcitabine	Gemcitabine Tamoxifen + P30 protein	150 patients with advanced pancreatic cancer	Closed No results
12. Trial of gemcitabine with or without CI994	Gemcitabine + CI994 capsules Gemcitabine + placebo	172 patients with advanced pancreatic cancer	Open No results
13. Trial of gemcitabine with or without R115777	Gemcitabine Gemcitabine + R115777	660 patients with advanced pancreatic cancer	Open No results
14. Trial of gemcitabine vs nitrocamptothecin	Oral nitrocamptothecin Gemcitabine	994 patients with unresectable locally advanced or metastatic adenocarcinoma of the pancreas	Open No results

continued

TABLE 11 *Features of completed RCTs versus ongoing RCTs: gemcitabine for pancreatic cancer (cont'd)*

Trial	Interventions	Participants	Completeness
15. Trial of nitrocamptothecin vs other chemotherapy	Oral nitrocamptothecin Other chemotherapy	400 patients with recurrent or refractory adenocarcinoma of the pancreas	Open No results
16. Trial of gemcitabine vs pancreatic proteolytic enzyme	Gemcitabine Pancreatic proteolytic enzyme therapy	72–90 patients with Stage II–III adenocarcinoma of the pancreas	Open No results
17. 93311L/0008	ZD9331 Gemcitabine	300 patients with pancreatic cancer	Open No results
18. EMD 121974-004	Gemcitabine + EMD121974 Gemcitabine	60 patients with pancreatic cancer	Open No results

observed significant result from available trials. In this case, the fail-safe N is

$$\text{FSN} = \frac{1 \times (2.81)^2}{(1.96)^2} - 1 \approx 1$$

That is, we need only one trial with a zero effect to change the significant result from the Burris trial into a non-significant result in meta-analysis. Therefore, the result from the Burris trial is not robust.

Bayesian data monitoring

Based on the survival curve presented in the Burris trial,[108] we roughly estimated that log(hazard ratio) is 0.471, with a standard error of 0.178 [i.e. $\sqrt{(4/126)}$]. To use Bayesian approaches, it is desirable to know what the 'minimal clinically worthwhile benefit' is. For example, it may be assumed that the minimal clinically worthwhile benefit equals a 20% reduction in death risk. Following the methods suggested by Fayers and colleagues,[106] a sceptical prior is arbitrarily presumed to have a mean log(hazard ratio) of zero, and the probability that an effect as large as or larger than $\log(h_1) = 0.2$ is $\gamma = 5\%$. Then,

$$\sigma_{\text{scep}} = \frac{\log(h_1)}{1.6445} = \frac{0.2}{1.6445} = 0.1216$$

So that

$$N_{\text{p}} = \frac{4}{\sigma_{\text{scep}}{}^2} = \frac{4}{0.1216^2} = 270$$

That is, the sceptical prior for log(hazard ratio) is specified as a normal distribution with a zero mean and a variance 4/270. Based on this sceptical prior distribution and observed data from the Burris trial, the posterior distribution of log(hazard ratio) is

$$\sim N\left[\frac{126 \times 0.471}{126 + 270},\ 4/(126 + 270)\right]$$

or

$$\sim N\,[0.15,\ 0.1005]$$

The sceptical, observed data and posterior distributions of log(hazard ratio) are presented in *Figure 6*. The posterior distribution is used to estimate the probabilities of log(hazard ratio) being greater than given values (*Table 12*). It can be seen from the table that there is reasonable (93%) evidence that log(hazard ratio) will be greater than zero. However, the evidence that log(hazard ratio) is >0.2 is small (31%).

Given the same observed data, any changes in sceptical prior distribution will result in different posterior probability. If we assume that the probability of a log(hazard ratio) being ≥0.4 (rather than 0.2 as before) is 5%, we actually increase the variance of prior distribution (new $N_{\text{p}} = 68$). Consequently, the impact of the prior distribution on the estimated posterior distribution is reduced, and the evidence will become more positive. For example, the probability of log(hazard ratio) being >0.2 increases from 31 to 77%.

The estimated posterior distributions suggest that the positive evidence from the Burris trial is not convincing. It is likely that the treatment with

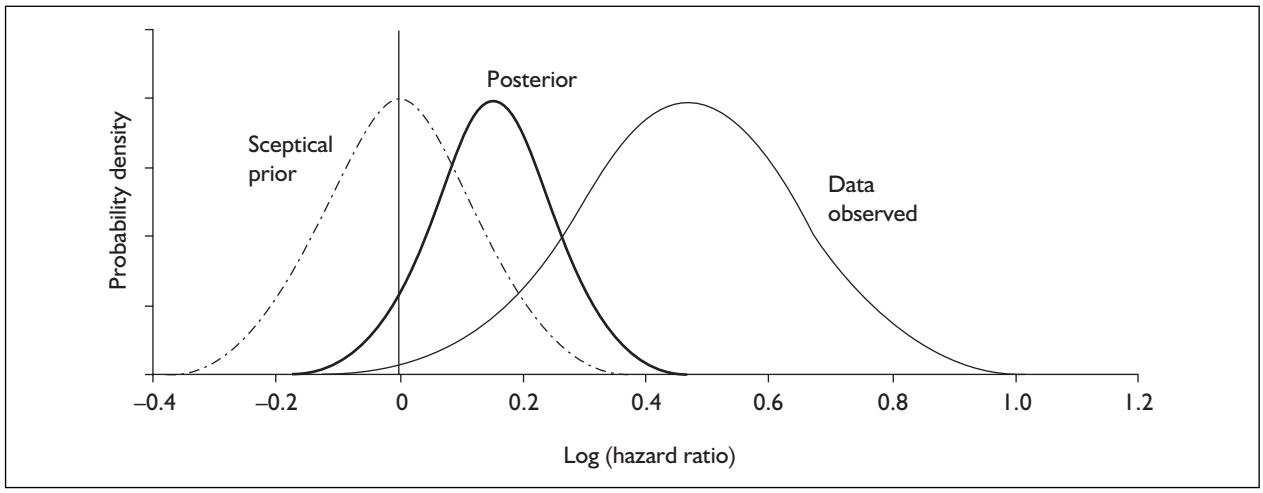

FIGURE 6 *Distribution of treatment effect: gemcitabine versus 5-FU for pancreatic cancer. Sceptical prior: mean = 0.0; assuming that the probability of an effect ≥0.2 is 5%. Observed log(hazard ratio) and its distribution were estimated from the survival curve in the Burris trial. The methods for calculations are based on Fayers and colleagues.*[106]

TABLE 12 *Probability of treatment effect being greater than a given level of log(hazard ratio) (a case study of gemcitabine for pancreatic cancer)*

Level of log(hazard ratio) (and hazard ratio)	Posterior probability[a] (%)
0.0 (1.00)	93.2
0.1 (1.11)	69.1
0.2 (1.22)	30.9
0.3 (1.35)	6.8
0.4 (1.49)	0.64
0.5 (1.65)	0.024
0.6 (1.82)	0.0004

[a] Based on the observed data and the sceptical prior that $\log(h_1) = 0.2$ and $\gamma = 5\%$.

gemcitabine for advanced pancreatic cancer is more efficacious than 5-FU in improving patients' survival, but the estimated treatment effect may be much smaller than that observed in the Burris trial. Evidence from further trials is needed to provide more convincing evidence about whether the treatment effectiveness is greater than the 'minimal clinically worthwhile benefit'.

Bayesian interim predictive probability

Data used for the calculations are summarised in *Table 13*. This method makes use of the number of events in ongoing trials ($n = 1060$). First, we estimate the probability that the final 95% CI will exclude zero (that is, $\delta_1 = 0$). Since

$$z_m(0) = \left(\frac{270 \times 0 + 126 \times 0.471}{270 + 126} - 0\right)\frac{\sqrt{270 + 126}}{2} = 1.49$$

so that

$$p_m\{P_{m+n}(0) < 0.025\} = \Phi\left\{1.49 \times \sqrt{\frac{270 + 126 + 1060}{1060}} - 1.96 \times \sqrt{\frac{270 + 126}{1060}}\right\} = \Phi(0.55) = 71\%$$

The result suggests that the probability that the final 95% CI (including data from further trials) will exclude zero (or show any improvement in the treatment arm) is 71%. If we assume that a minimally meaningful benefit is equivalent to a log(hazard ratio) of 0.2, the predictive probability that the final 95% CI will exclude this value is only 3.7%. Therefore, the existing evidence is not convincing and findings from ongoing trials are required to confirm the significant result from the Burris trial.

In *Figure 7*, the estimated conditional power that the final 95% CI will exclude a log(hazard ratio) of 0.2 is illustrated by both the full Bayesian approach and the mixed approach. The calculations can be carried out by the BANDY (Bayesian Analysis using Normal Distributions) Excel program (available from http://www.mrc-bsu.cam.ac.uk/bayeseval/, the website for a new book on Bayesian approaches to clinical trials and healthcare evaluation by Spiegelhalter and colleagues[109]).

Case study summary

A total of 12 ongoing RCTs were listed in the HTAR, although only three were relevant for the

TABLE 13 *Data used for Bayesian interim prediction (a case study of gemcitabine for pancreatic cancer)*

Description	Value
Prior mean	$\delta_0 = 0$
Number of events for prior distribution	$n_0 = 270$
Standard deviation for prior distribution	$\sigma = 2$
Statistical significance	$2\varepsilon = 0.05$ or $Z_{0.05} = 1.96$
Number of observed events (in completed trials)	$m = 126$
Observed mean log (hazard ratio)	$X_m = 0.471$
Number of events in ongoing trials	$n = 1060$

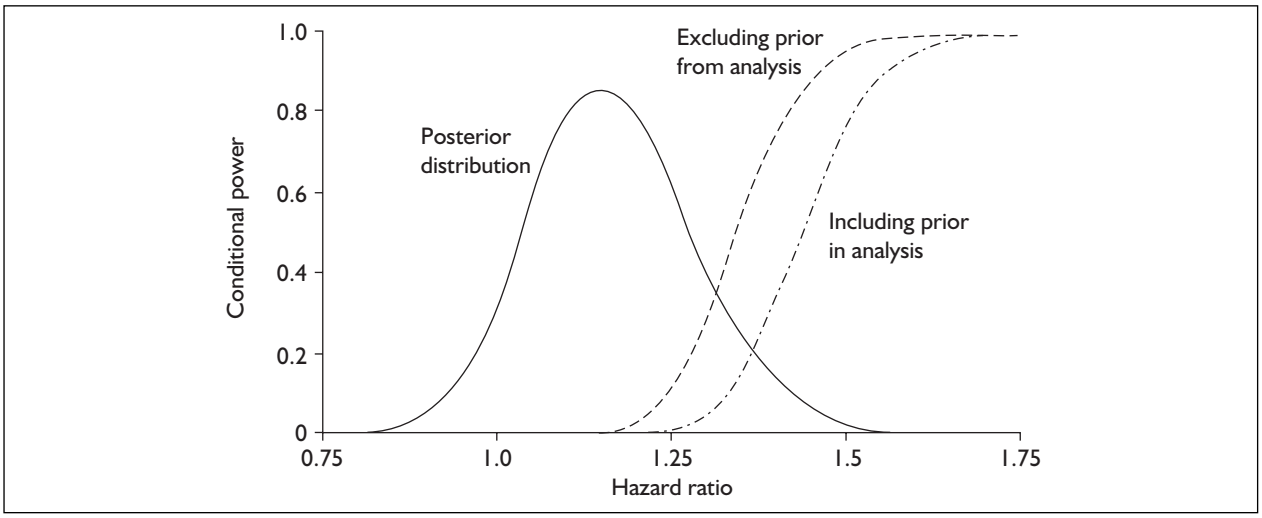

FIGURE 7 *Estimated conditional power – Bayesian interim prediction (a case study of gemcitabine vs 5-FU for pancreatic cancer; $\delta_I = 0.2$)*

comparison of gemcitabine and 5-FU directly. We have not considered much about the qualitative comparison in this case study. The qualitative assessment of ongoing trials should be best carried out by the original HTAR team since thorough knowledge about the topics is required. We have applied different quantitative methods to estimate the possible impacts of ongoing trials (or robustness of the available evidence). Results of the quantitative analyses consistently suggest that the available evidence from the single trial is not convincing and there is great possibility that different results may be obtained if data from ongoing trials become available.

The authors of the original HTAR[107] concluded that there was a very poor evidence base by which to assess the efficacy of gemcitabine; and the validity of the only RCT that compared gemcitabine with the standard treatment of 5-FU was open to question. They correctly focused on the design features of the Burris trial and the small number of patients included in the trial. Their conclusion could be further strengthened by quantitative assessment of the possible impact of ongoing trials.

Chapter summary

The first stage of assessing the possible impact of ongoing trials is qualitative in nature. The qualitative assessment of ongoing trials involve mainly a comparison of major features of completed and ongoing trials. It provides qualitative information about the possible impact of ongoing trials in terms of relevance, validity, reliability and generalisability. The most crucial question is whether the objectives of ongoing trials are the same as that of completed trials, which may be specified from three dimensions: trial participants, interventions (including comparators) and outcomes measured. Design quality and other issues such as the follow-up duration may also be important.

To assess quantitatively the impact of ongoing trials is to predict the possible changes in estimated treatment effect when data from ongoing trials become available. The impact of ongoing trials will be considerable if they are large and well designed. The impact of ongoing trials will be particularly important when evidence from existing trials is inconclusive. This is why methods

TABLE 14 *Summary of quantitative methods that may be useful for assessing the impact of ongoing trials*

Method	Objectives	Data required from existing trials	Data required from ongoing trials	Subjective judgement required	Assessment of impact of ongoing trials
Sequential monitoring boundaries	To provide monitoring boundaries in cumulative meta-analysis, to deal with inflated Type I error due to multiple statistical testing	Number of patients and cumulative z score	Number of patients	Presumed 'true treatment effect' or 'minimal worthwhile effect' may be used to estimate 'optimal information size'. Level of Type I and II error	If the observed cumulative z value is below the monitoring boundaries, the evidence from completed trials is not conclusive and further evidence from ongoing trials is important
Stochastic curtailment	To predict the probability of rejecting the null hypothesis when all information becomes available, given the current data and assuming that the null hypothesis is true	Number of patients and cumulative z score	Number of patients	Presumed 'true treatment effect' or 'minimal worthwhile effect' may be used to estimate 'optimal information size' Level of Type I and II error	If the conditional probability to reject the null hypothesis is small or modest, the evidence from completed trials is inconclusive and further evidence from ongoing trials is important
Fail-safe N	To estimate the number of additional studies (fail-safe N) required to overturn the significant result from completed trials	Number of completed trials and cumulative z score	Not required	The tolerance level of fail-safe N. A value of $5k + 10$ had been arbitrarily suggested Level of Type I error	If a large number of additional trials will be required to overturn the positive finding, the existing evidence could be considered robust. If the fail-safe N is small, the statistically significant result from completed trials can be easily overturned by additional trials and the possible impact of ongoing trials should not be ignored
Bayesian data monitoring	To prevent overenthusiastic acceptance of positive findings from early trials, by incorporating a sceptical prior	Information size (number of events for survival analysis) from completed trials and observed treatment effect, e.g. log(hazard ratio)	Not required	Sceptical prior distribution assumes that the treatment effect is zero but there is a small possibility that it is as large as or greater than a value of alternative hypothesis (such as the minimal clinically worthwhile benefit)	The positive evidence from completed trials is considered inconclusive if there is only a small or modest posterior probability that the treatment effect will be as large as or greater than the minimal clinically worthwhile benefit
Bayesian predictive probability	To predict the probability that a final confidence interval will exclude a chosen value of treatment effect	Information size (or number of events for survival analysis) from completed trials and observed treatment effect, e.g. log(hazard ratio)	Information size (or estimated number of events for survival analysis)	Sceptical prior distribution assumes that the treatment effect is zero but there is a small possibility that it is as large as or greater than a value of alternative hypothesis (such as the minimal clinically worthwhile benefit)	The positive finding from the completed trials is inconclusive if the predictive probability that the final CI will exclude zero or the minimal worthwhile benefit is small or modest

that assess the conclusiveness of existing evidence may be useful for the assessment of the possible impact of ongoing trials.

Table 14 summarises the quantitative methods that may be useful for the assessment of impact of ongoing trials. These methods are mainly based on the observed treatment effect and the number of patients (or events) in existing trials. Data from ongoing trials are not necessary for methods that only assess the robustness or conclusiveness of existing evidence (fail-safe N, Bayesian data monitoring). The number of patients in ongoing trials may be useful but not essential (provided that OIS could be estimated) in the use of sequential monitoring boundaries and stochastic curtailment method. The Bayesian predictive probability method makes use of data (number of patients/events) from ongoing trials. All methods require subjective judgement about levels of Type I and II error and/or minimal clinically worthwhile benefit and/or presumed prior distribution of the parameter. The methods of quantitative assessment focus mainly on the robustness or conclusiveness of existing evidence. Stochastic curtailment and Bayesian predictive probability could provide some estimates about the range of final CIs when data from ongoing trials become available, under certain assumptions.

In the case study, the different quantitative methods provided consistent conclusions about the importance of ongoing trials. The most useful method may be the Bayesian predictive probability. This method can provide predictive probabilities for any possible values of treatment effect and it uses available data more completely including sceptical prior distribution, observed data and information about ongoing trials. Appropriate use of quantitative methods will strengthen findings from qualitative assessment about the possible impact of ongoing trials.

Chapter 6

Discussion and conclusions

To answer methodological questions about ongoing trials in effectiveness reviews, we surveyed a sample of completed HTARs, reviewed methodological studies and carried out case studies. We found that the identification of ongoing trials was a common phenomenon in HTARs. Twenty-three of the 32 HTARs included in the survey identified one or more ongoing trials. This phenomenon was not clearly associated with any HTAR characteristics, such as disease or technology categories, explicitness of search strategies, convincingness of HTAR conclusions and number of studies included.

Searching for ongoing trials

There are a large number of trial registers (international or national, general or subject-specific). The development of information technology has greatly improved access to numerous sources of information on ongoing trials, particularly the web-based trial registers. The assessment of six commonly used trial registers (Chapter 4) suggested that most registers provided sufficient information for reviewers to decide the relevance of identified ongoing trials. However, it is sometimes extremely difficult to know whether ongoing trials identified from different sources (registers) are the same trials or belong to the same multicentre trials. The ISRCTN would make cross-reference easier but it has not yet been widely adopted.

Search strategies currently employed by HTAR teams are capable of locating ongoing trials. All 32 HTARs searched for unpublished studies, ongoing trials or grey literature and studies in trial registers. The awareness of unpublished studies and efforts made to search for unpublished trials or grey literature may result in the identification of ongoing trials. Trial registers and grey literature are important sources of information on ongoing trials (see Chapter 4). Therefore, it is not surprising that a search of grey literature and trial registers may locate ongoing trials, no matter whether the search for ongoing trials was explicit or not. However, the explicit reporting of searches for ongoing trials is important for quality assessing systematic reviews. In particular, the thoroughness of searches for ongoing trials needs to be assessed. In the two case studies of locating ongoing trials in Chapter 4, the search of trial registers *m*RCT and NRR would identify some relevant ongoing trials, but a significant number of additional trials were identified by searching additional sources (see *Table 9*).

Incorporating ongoing trials in HTARs

It is a difficult task to incorporate information from identified ongoing trials in HTARs. Twenty-three of the 32 HTARs identified ongoing trials. In eight of the 23 HTARs with ongoing trials, the information on identified ongoing trials was not considered in the evidence synthesis and research recommendations. Of the remaining 15 HTARs with ongoing trials, 12 attempted to consider the impact of ongoing trials on conclusions, eight on research recommendations and only three incorporated information on ongoing trials in the results synthesis. All but one HTAR that considered the potential impact of ongoing trials adopted a narrative approach.

Qualitative assessment of identified ongoing trials and narrative approaches to incorporating information on ongoing trials seems likely to remain the dominant approaches in effectiveness reviews. However, the qualitative assessment of identified ongoing trials could be more explicit and structured, as suggested in Chapter 5. It involves mainly a comparison of major features (for example, patients, interventions, outcomes and study designs) of completed and ongoing trials. Systematic reviewers need to provide an explicit judgement about the relevance and possible impact of expected results of ongoing trials.

For example, in a recently completed HTAR of imatinib for GISTs (case study I in Chapter 4),[110] we assessed identified ongoing trials. Like the trials that have been completed, the ongoing trials were uncontrolled. However, these ongoing trials provide additional information on a greater number of imatinib-treated patients and longer follow-up. We considered the possible impact of these ongoing trials in our conclusions and

research recommendations. We believe that explicit presentation of information on ongoing trials will help the NICE technology appraisal committee and other users of HTARs to assess the robustness of the conclusions and decide whether and when the review needs to be updated.

Only one of the 32 HTARs quantitatively assessed the impact of identified ongoing trials. In an HTAR of zanamivir for the treatment of influenza in adults,[30] sensitivity analysis was carried out to test the robustness of the pooled effect size to possible negative results of three ongoing trials.

In Chapter 5, we reviewed available quantitative methods that may be used to assess the impact of ongoing trials. Subjective judgement is required by all the methods, for example, about levels of Type I and II error, minimal clinically worthwhile benefit and presumed prior distribution of the parameter. The fail-safe N method and Bayesian data monitoring method do not directly use information on ongoing trials, but focus on the assessment of the conclusiveness of existing evidence. The number of patients in ongoing trials is required by cumulative meta-analysis-related methods (sequential monitoring boundaries and stochastic curtailment method). The most useful method may be the Bayesian predictive probability. This method can provide predictive probabilities for any possible values of treatment effect and it uses available data more completely, including sceptical prior distribution, observed data and information about ongoing trials.

Main limitations

We searched several commonly used literature databases for relevant methodological studies (Chapter 2). The literature search could be more comprehensive by covering additional databases (for example, we did not search abstracts of the meetings of the International Society for Clinical Biostatistics). The literature search presented in Chapter 2 should be considered as a preliminary effort to identify relevant studies. In this report, the search for relevant methodological studies was actually a continuous and iterative process, performed by authors who were involved in the subsequent chapters.

Our survey of ongoing trials in effectiveness reviews was limited to a sample of HTA reviews for NICE. However, it is likely that ongoing trials are also common in other systematic reviews (for example, Cochrane Systematic Reviews). There is no reason to believe that issues in the identification and assessment of ongoing trials in HTA reviews for NICE will be different from most systematic reviews under other circumstances. Therefore, findings from this methodological review will also be relevant to any literature reviews of effectiveness and cost-effectiveness of healthcare interventions.

In a case study in Chapter 5, we found that the different quantitative methods provided consistent conclusions about the importance of ongoing trials, and appropriate use of quantitative methods would strengthen findings from narrative assessment of possible impact of ongoing trials. The usefulness and limitations of the available methods need to be tested in more effectiveness reviews.

Conclusions

Clinical and policy decisions on healthcare interventions have to be made according to the best currently available evidence. However, the evidence base evolves over time. Knowledge about the existence of ongoing trials and considering their possible impact on research evidence will help decision-makers to understand how confident or tentative their decisions must be. The awareness and assessment of ongoing research may result in more appropriate decisions about whether and when a completed HTAR should be updated. Any recommendations for further trials should also consider trials in progress.

Identification of ongoing trials is common in health technology assessment reviews. Searching for ongoing trials in effectiveness reviews should be more thorough and explicit. Conversely, primary researchers, in particular those working within multicentre trials, should label ongoing trials more clearly, preferably by ISRCTN. Qualitative assessment of identified ongoing trials is crucial and informative. Available quantitative methods could be used to strengthen findings from narrative assessment, although further research and more empirical examples are required. Information from ongoing trials may contribute to syntheses of results, conclusions and recommendations for future research.

Recommendations for future research

The following areas are suggested for further research.

- Identification and assessment of ongoing trials in other systematic reviews of effectiveness of healthcare interventions (for example, Cochrane Systematic Reviews) should be evaluated.
- Existing and new qualitative and quantitative methods for incorporating information on ongoing trials need to be tested and compared in further effectiveness reviews and/or computer simulation studies.
- The validity of estimated impacts of ongoing trials could be evaluated by comparing estimated impacts with the actual results of ongoing trials. This could be done prospectively with long-term follow-up of selected HTARs. A retrospective study would also be possible by examining the evolution of trial evidence for selected topics.
- Further research is required to incorporate findings from the assessment of ongoing trials into decision models. For example, posterior predictive distribution may be useful for dealing with uncertainty problems in cost-effectiveness modelling.

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About 'home unit'

The Department of Public Health and Epidemiology, University of Birmingham, produces health technology assessment reviews, in response to requests from West Midlands NHS and the NCCHTA programme.

Contributions of authors

F Song (Reader in Research Synthesis) developed, and C Hyde (Senior Clinical Lecturer) and A Fry-Smith (Information Specialist) commented on the research protocol. A Fry-Smith and S Bayliss (Information Specialist) searched electronic literature databases, evaluated trial registers, and wrote Chapter 4. Y Adi (Systematic Reviewer), C Davenport (Clinical Research Fellow) and F Song assessed the results of the literature searches. JS Wilson (Systematic Reviewer), C Davenport, Y Adi, C Hyde and F Song assessed and extracted data from included HTARs. C Davenport and F Song summarised the survey of completed HTARs and C Davenport drafted Chapter 3. F Song wrote Chapter 5 and took the responsibility for the final report.

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References

1. Hill S, Garattini S, van-Loenhout J, O'Brien BJ, de-Joncheere K. *Technology appraisal programme of the National Institute for Clinical Excellence – a review by WHO*. Geneva: World Health Organization (Europe), 2003.
2. Khan K, ter-Riet G, Glanville J, Sowden AJ, Kleijnen J. *Undertaking systematic reviews of research on effectiveness – CRD's guidance for those carrying out or commissioning reviews*. York: Centre for Reviews and Dissemination, University of York; 2001.
3. Clarke M, Oxman AD. Cochrane Reviewers' Handbook 4.2.0 [updated March 2003]. *The* (*Cochrane Library*) Issue 2. Oxford: Update Software; 2003.
4. Piantadosi S. *Clinical trials – a methodologic perspective*. New York: John Wiley; 1997.
5. Berry DA. Basic principles in designing and analyzing clinical studies. In Berry DA, editor. *Statistical methodology in the pharmaceutical science*. New York: Marcel Dekker; 1990. pp. 1–55.
6. Bakke OM, Manocchia M, de Abajo F, Kaitin KI, Lasagna L. Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: a regulatory perspective. *Clin Pharmacol Ther* 1995;**58**:108–17.
7. Borzak S, Ridker PM. Discordance between meta-analyses and large scale randomized, controlled trials; examples from the management of acute myocardial infarction. *Ann Intern Med* 1995;**123**:873–7.
8. Fletcher A, Spiegelhalter D, Staessen J, Thijs L, Bulpitt C. Implications for trials in progress of publication of positive results. *Lancet* 1993; **342**:653–7.
9. Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomized trials. *J R Stat Soc A* 1994;**157**:357–416.
10. Song F, Eastwood A, Gilbody S, Duley L, Sutton A. Publication and related biases. *Health Technol Assess* 2000;**4**(10).
11. Olsen KL, Hopewell S, Dickersin K, Clarke M, Oxman AD. Publication bias in clinical trials. *The Cochrane Library*. Issue 3. Oxford: Update Software, 2002.
12. Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. *The Cochrane Library*. Issue 3. Oxford: Update Software, 2002.
13. Cappelleri JC, Ioannidis JP, Schmid CH, de Ferranti SD, Aubert M, Chalmers TC, *et al*. Large trials vs meta-analysis of smaller trials: how do their results compare? *JAMA* 1996;**276**:1332–8.
14. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997;**337**:536–42.
15. Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. *Lancet* 1995;**345**:772–6.
16. Scott R. Answering the unanswered questions: ongoing trials of statins and antihypertensives in type 2 diabetes. *Acta Diabetol* 2002; **39** Suppl 2:S46–51.
17. 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, editors. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 2000. pp. 429–43.
18. Laupacis A, Connolly SJ, Gent M, Roberts RS, Cairns J, Joyner C. How should results from completed studies influence ongoing clinical trials? The CAFA Study experience. *Ann Intern Med* 1991;**115**:818–22.
19. 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. *Control Clin Trials* 1988;**9**:76–81.
20. Manheimer E, Anderson D. Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility. *BMJ* 2002;**325**:528–31.
21. Carpenter LM. Is the study worth doing? *Lancet* 1993;**342**:221–3.
22. Parmar MKB, Ungerleider RS, Simon R. Assessing whether to perform a confirmatory randomized clinical trial. *J Nat Cancer Inst* 1996;**88**:1645–51.
23. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. *Stat Methods Med Res* 2000;**9**:421–45.
24. 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.

25. Song F, Sheldon TA, Sutton AJ, Abrams KR, Jones DR. Methods for exploring heterogeneity in meta-analysis. *Eval Health Profess* 2001;**24**:126–51.

26. Abrams K, Ashby D, Errington D. Simple Bayesian analysis in clinical trials: a tutorial. *Control Clin Trials* 1994;**15**:349–59.

27. Claxton K, Neumann PJ, Araki S, Weinstein MC. Bayesian value-of-information analysis: an application to a policy model of Alzheimer disease. *Int J Technol Assess Health Care* 2001;**17**:38–55.

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

29. Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*. Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(18).

30. Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*. Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(9).

31. Chilcott J, Wight J, Lloyd JM, Tappenden P. The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review. *Health Technol Assess* 2001; **5**(19).

32. Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer. *Health Technol Assess* 2001;**5**(32).

33. Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*. The clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review. *Health Technol Assess* 2001;**5**(1).

34. Clegg A, Bryant J, Milne R. Disease-modifying drugs for multiple sclerosis: a rapid and systematic review. *Health Technol Assess* 2000;**4**(9).

35. Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A. The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(12).

36. Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. *Health Technol Assess* 2002;**6**(17).

37. Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*. The management of dyspepsia: a systematic review. *Health Technol Assess* 2000;**4**(39).

38. Dinnes J, Cave C, Huang S, Major K, Milne R. The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review. *Health Technol Assess* 2001;**5**(13).

39. Forbes C, Shirran L, Bagnall AM, Duffy S, ter Riet G. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer. *Health Technol Assess* 2001;**5**(28).

40. Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*. Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment. *Health Technol Assess* 2002;**6**(2).

41. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(21).

42. Jobanputra P, Parry D, Fry-Smith A, Burls A. Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review. *Health Technol Assess* 2001;**5**(11).

43. Lewis R, Bagnall AM, King S, Woolacott N, Forbes C, Shirran L, *et al*. The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(14).

44. Lewis R, Bagnall AM, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*. The clinical effectiveness of trastuzumab for breast cancer: a systematic review. *Health Technol Assess* 2002;**6**(13).

45. Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention. *Health Technol Assess* 2001;**5**(14).

46. Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J. A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. *Health Technol Assess* 2000;**4**(17).

47. Lloyd JM, Hummel S, Bansback N, Orr B, Seymour M. A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. *Health Technol Assess* 2001;**5**(25).

48. McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G. A rapid and systematic

review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina. *Health Technol Assess* 2000;**4**(30).

49. Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. *Health Technol Assess* 2000;**4**(23).

50. O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G. The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment. *Health Technol Assess* 2002;**6**(6).

51. O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity. *Health Technol Assess* 2001;**5**(18).

52. Parkes J, Bryant J, Milne R. Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review. *Health Technol Assess* 2000;**4**(26).

53. Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess* 2000;**4**(18).

54. Peters J, Stevenson M, Beverley C, Lim JN, Smith S. The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(5).

55. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technol Assess* 2000;**4**(33).

56. Song F, O'Meara S, Wilson P, Golder S, Kleijnen J. The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth. *Health Technol Assess* 2000;**4**(15).

57. Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*. The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review. *Health Technol Assess* 2001;**5**(2).

58. Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC. A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease. *Health Technol Assess* 2002;**6**(15).

59. Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*. Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(3).

60. Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*. The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(16).

61. McNamee D. Review of clinical protocols and *The Lancet*. *Lancet* 2003;**357**:1819.

62. Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003;**290**:516–23.

63. Tonks A. Registering clinical trials. *BMJ* 1999; **319**:1565–8.

64. Current controlled trials' strategy for supporting the continued development of the mRCT and ISRTN scheme CCT strategic review. 2001.

65. Marley C, Godlee F, Chalmers I. An International MetaRegister and unique identification system for randomised trials. *Control Clin Trials* 2001;**22**:33S.

66. Fayers P. UKCCR Register of UK Cancer Trials. *Control Clin Trials* 1995;**16**:172–81.

67. Chollar SA. A registry for clinical trials. *Ann Intern Med* 1998;**128**:701–2.

68. Lee H. The EU-PSI project: the story so far. *Cochrane Dementia and Cognitive Improvement Group Newsletter* 2001;(5):4–5.

69. Krzyzanowska MK, Pintilie M, Tannock IF. Factors associated with failure to publish large randomized trials presented at an oncology meeting. *JAMA* 2003;**290**:495–501.

70. Scherer R, Langenberg P. Full publication of results initially presented in abstract: revisited (Cochrane Methodology Review). *The Cochrane Library*. Issue 1. Chichester: John Wiley; 2004.

71. Glanville J. *Finding trials on the Internet: selected resources*. York: University of York, NHS Centre for Reviews and Dissemination; 2002.

72. Royle P, Bidwell S. Searching for randomised controlled trials in meeting abstracts. *Health Technol Assess (ISTACH Newsletter)* 2000;5.

73. Vickers AJ, Smith C. Incorporating data from dissertations in systematic reviews. *Int J Technol Assess Health Care* 2000;**16**:711–13.

74. MacLean H, Morton SC, Ofman J, Roth ER, Shekelle PG. How useful are unpublished data from the Food and Drug Administration in meta-analysis? *J Clin Epidemiol* 2003;**56**:44–51.

75. Bennett DA, Jull A. FDA: untapped source of unpublished trials. *Lancet* 2003;**361**:1402–3.

76. Moore A, McQuay H. Mindstretcher – does unpublished information make a difference? *Bandolier* 2003;**110**:5.

77. Roberts I, Po AL, Chalmers I. Intellectual property, drug licensing, freedom of information, and public health. *Lancet* 1998;**352**:726–9.

78. Gibbs TE, Wager E. Realities of trial registration: the Glaxo Wellcome experience. *Int J Pharm Med* 2000;**14**:203–5.

79. Sykes R. Being a modern pharmaceutical company: involves making information available on clinical trial programmes. *BMJ* 1998;**317**:1172.

80. Pharmaceutical industry leads world in launching scheme to register clinical trials in UK. *Cochrane News* 2000;(4).

81. Eysenbach G, Wyatt J. Using the internet for surveys and health research. *J Med Internet Res* 2002;**4**:E13.

82. Adelhard K, Obst O. Evaluation of medical internet sites. *Methods Inf Med* 1999;**38**:75–9.

83. Wyatt JC. Commentary: measuring quality and impact of the world wide web. *BMJ* 1997; **314**:1879–81.

84. Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003;**7**(1).

85. Savoie I, Helmer D, Green CJ, Kazanjian A. Beyond Medline: reducing bias through extended systematic review search. *Int J Technol Assess Health Care* 2003;**19**:168–78.

86. Suarez-Almazor ME, Belseck E, Homik J, Dorgan M, Ramos RC. Identifying clinical trials in the medical literature with electronic databases: MEDLINE alone is not enough. *Control Clin Trials* 2000;**21**:476–87.

87. Royle P, Milne R. Literature searching for randomised controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *Int J Technol Assess Health Care* 2003;**19**:591–603.

88. Chan AW, and Altman DG. Discrepancies between protocols and publications: evidence of outcome reporting bias in randomised trials. Presented at the XI Cochrane Colloquium – Evidence, Health Care and Culture. Barcelona; 26–31 October, 2003.

89. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;**317**:1185–90.

90. Song F, Glenny AM, Altman DG. Indirect comparison in evaluating relative efficacy illustrated by antimicrobial prophylaxis in colorectal surgery. *Control Clin Trials* 2000; **21**:488–97.

91. Gotzsche PC, Liberati A, Torri V, Rossetti L. Beware of surrogate outcome measures. *Int J Technol Assess Health Care* 1996;**12**:238–46.

92. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;**285**:1987–91.

93. Juni P, Altman D, Egger M. Systematic reviews in health care – assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–6.

94. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;**327**:248–54.

95. Ioannidis JPA, Contopoulos DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. *J Clin Epidemiol* 1999;**52**:281–91.

96. Henderson WG, Moritz T, Goldman S, Copeland J, Sethi G. Use of cumulative meta-analysis in the design, monitoring, and final analysis of a clinical trial: a case study. *Control Clin Trials* 1995;**16**:331–41.

97. Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci USA* 2001;**98**:831–6.

98. Mullen B, Muellerleile P, Bryant B. Cumulative meta-analysis: a consideration of indicators of sufficiency and stability. *Pers Soc Psychol Bull* 2001;**27**:1450–62.

99. Pogue JM,Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997;**18**:580–93.

100. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; **3**:659–63.

101. Halperin M, Lan KK, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. *Control Clin trials* 1982; **3**:311–23.

102. Lan KKG, Wittes J. The B-value: a tool for monitoring data. *Biometrics* 1988;**44**:579–85.

103. Rosenthal R. The "file drawer problem" and tolerance for null results. *Psychol Bull* 1979; **86**:638–41.

104. Carson KP, Schriesheim CA, Kinicki AJ. The usefulness of the "fail-safe" statistic in meta-analysis. *Educ Psychol Meas* 1990;**50**:233–43.

105. Spiegelhalter DJ, Myles PJ, Jones DR, Abrams KR. An introduction to bayesian methods in health technology assessment. *BMJ* 1999;**319**:508–12.

106. Fayers PM, Ashby D, Parmar MKB. Tutorial in biostatistics. Bayesian data monitoring in clinical trials. *Stat Med* 1997;**16**:1413–30.

107. Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*. A rapid and systematic

review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer. *Health Technol Assess* 1997;**5**(24).

108. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, *et al*. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;**15**:2403–13.

109. Spielgelhalter D, Abrames KR, Myles JP. *Bayesian approaches to clinical trials and health-care evaluation*. WileyEurope; 2003.

110. Wilson J, Connock M, Song FJ, Yao G, Fry-Smith A, Raftery J, *et al*. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: a systematic review and economic evaluation. *Health Technol Assess* in press.

Appendix 1

Search strategy for relevant literature

Electronic databases

MEDLINE from 1966 to December 2002	Cochrane Library Methodological Database
1 ongoing clinical trial$.ti,ab. 2 ongoing trial$.ti,ab. 3 ongoing drug trial$.ti,ab. 4 trial$ in progress.ti,ab. 5 clinical trial$ in progress.ti,ab. 6 phase I.mp. 7 phase II.mp. 8 phase III.mp. 9 phase IV.mp. 10 clinical trials phase I/ 11 clinical trials phase II/ 12 clinical trials phase III/ 13 clinical trials phase IV/ 14 (unpublished adj1 trial$).ti,ab. 15 trial$ regist$.ti,ab. 16 registries/ 17 or/1-16 18 meta-analysis/ 19 review literature/ 20 meta-analys$.ti,ab. 21 systematic review$.ti,ab. 22 publication bias.mp. 23 or/18-22 24 17 and 23	Ongoing CMR (PROSPECTIVE next REGISTRATION) (SEARCH next STRATEGIES) TRIAL* (#3 and #4) (ONGOING near TRIAL*) (UNPUBLISHED near TRIAL*) (UNPUBLISHED next DATA) ((((#2 or #5) or #6) or #7) or #8) (#1 and #9) ((#6 or #7) or #8) (#1 and #11)

List of journals, textbooks and conference proceedings that were hand searched:

- *Controlled Clinical Trials*, 1981–2002
- *Journal of Clinical Epidemiology*, 1995–2002
- *Statistics in Medicine*, 1996–2002
- *International Journal of Technology Assessment in Health Care*, 1995–2002
- Egger M, Davey-Smith G, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 2000.
- Black N, Brazier J, Fitzpatrick R, Reeves B, editors. *Health services research methods: a guide to best practice*. London: BMJ Books; 1998. pp. 255–9.
- Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R. *The advanced handbook of methods in evidence based healthcare*. London: Sage Publications; 2001.
- Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for meta-analysis in medical research*. Chichester: Wiley; 2000.
- Cooper H, Hedges LV, editors. *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*. York: University of York; 2001.
- *Cochrane Reviewers' Handbook 4.1*. Oxford: The Cochrane Collaboration; 2000
- *Symposia on Systematic Reviews*, Oxford: Centre for Statistics in Medicine; 1999–2002
- *Cochrane Collaboration Colloquia*, 2000–01
- *The International Society of Technology Assessment in Health Care*, 1995–2002

Appendix 2

List of studies identified by the first stage of literature search

Balas EA, Mitchell JA, Bopp K, Brown GD, Ewigman BT. The Columbia Registry of Controlled Clinical Computer Trials. *Proc Annu Symp Comput Appl Med Care* 1992; 220–4.

Balas EA, Stockham MG, Mitchell JA, Austin SM, West DA, Ewigman BT. The Columbia Registry of information and utilization management trials. *J Am Med Inf Assoc* 1995;**2**:307–15.

Bates R, Bertelsen J, Chauvette P, Hastings J, Strouse D. Development of a centralized trials registry for research on HIV/AIDS prevention. *In 6th Annual Cochrane Colloquium Abstracts*. Baltimore; 1998.

Bennett DA, Jull A. FDA: untapped source of unpublished trials. *Lancet* 2003;**361**:1402–3.

Bonati M. Is it time for a registry of clinical trials in pediatrics? *J Pediatr* 1990;**116**:667–8.

Bosch X. The publication in biomedical journals of clinical trial protocols: a new way to improve research quality (editorial). *Rev Esp Cardiol* 1999;**52**:359–61 (in Spanish).

Brundage MD, Mackillop WJ. Locally advanced non-small cell lung cancer: do we know the questions? A survey of randomized trials from 1966–1993. *J Clin Epidemiol* 1996;**49**:183–92.

Burdett S, Stewart LA. Publication bias and meta-analysis: a practical example. *In 8th Annual Cochrane Colloquium Abstracts*. Cape Town; 2000.

Burrett J. Identification of randomised trials for inclusion in meta-analyses of treatments for childhood acute lymphoblastic leukaemia. *The Cochrane Library*. Oxford: Update Software; 2001.

Buyse M, Firket P, De Conick A, Staquet M. EUROCODE: a computerized network for clinical trials in oncology [abstract]. *Control Clin Trials* 1988;**9**:259.

Buyse M. Interim analyses, stopping rules and data monitoring in clinical trials in Europe. *Stat Med* 1993;**12**:509–20.

Campbell OJ, Daly C, Cody J, Khan IH, Campbell MK, Wallace SA, *et al*. Surfing systematically – experience of searching the internet. Presented at the First Symposium on Systematic Reviews: Beyond the Basics. Oxford; 1998.

Chalmers I, Hetherington J, Newdick M, Mutch L, Grant A, Enkin M, *et al*. The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. *Control Clin Trials* 1986;**7**:306–24.

Chernoff MC, Wang M, Anderson JJ, Felson DT. Problems and suggested solutions in creating an archive of clinical trials data to permit later meta-analysis: an example of methotrexate trials in rheumatoid arthritis. *Control Clin Trials* 1995;**16**:342–55.

Cholesterol TT. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. Cholesterol Treatment Trialists' (CTT) Collaboration. *Am J Cardiol* 1995;**75**:1130–4.

Cook DJ, Guyatt GH, Ryans G, Clifton J. Should unpublished data be included in meta-analyses? *JAMA* 1993;**269**:2753.

DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. *Stat Med* 1996;**15**:1237–48.

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. *Control Clin Trials* 1988;**9**:76–81.

Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990;**263**:1385–9.

Dickersin K. Keeping posted. Why register clinical trials? – revisited. *Control Clin Trials* 1992;**13**:170–7.

Dickersin K, Min YI. NIH clinical trials and publication bias. *Online J Curr Clin Trials* 1993; Doc. No. 50.

Easterbrook PJ. Directory of registries of clinical trials. *Stat Med* 1992;**11**:363–423.

Egger MJ. Importance of different sources of bias in systematic reviews of controlled trials: systematic review of empirical studies. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

Enkin M, Hetherington J. Collecting the evidence systematically. Ensuring that it is complete and up-to-date. *Int J Technol Assess Health Care* 1996;**12**:276–9.

Eysenbach G. Use of the world-wide-web to identify unpublished evidence for systematic reviews – the future role of the Internet to improve information identification. In *7th Annual Cochrane Colloquium Abstracts*. Rome; 1999.

Eysenbach G, Tuische J, Diepgen TL. Evaluation of the usefulness of Internet searches to identify unpublished clinical trials for systematic reviews. *Med Inf Internet Med* 2001;**26**:203–18.

Fernandes RL, Castro AA, Clark OAC, Iochida LC, Atallah AN. Improving retrieval of clinical trials in the LILACS database. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

Fletcher A, Spiegelhalter D, Staessen J, Thijs L, Bulpitt C. Implications for trials in progress of publication of positive results. *Clin Trials* 1993; **342**:653–7.

Fossati R, Confalonieri C, Torri V, Liberati A. Meta-analyses of published results are unreliable – reply. *J Clin Oncol* 1999;**17**:1647.

Gtzsche PC, Olsen O. Misleading publications of major mammography screening trials in major general medical journals. Presented at the 4th International Congress on Peer Review in Biomedical Publication. Barcelona; 2001.

Gould AL, Shih WJ. Modifying the design of ongoing trials without unblinding. *Stat Med* 1998;**17**:89–100.

Grosse M, Hogsdon SN, Stewart LA. The return of the register: the UKCCCR Register of Cancer Trials. Presented at the 2nd International Conference on Scientific Basis of Health Services and 5th Annual Cochrane Colloquium. Amsterdam; 2001.

Harlan WR. Creating an NIH clinical trials registry: a user-friendly approach to health care. *JAMA* 1994; **271**:1729.

Hawkins BS, Optican DC, *et al*. Archives for data and documents from completed clinical trials: how are they maintained and how have they been used? [abstract]. *Control Clinical Trials* 1986;**7**:244–5.

Hawson S, Hannah M, Fried B, Hellmann J, Naglie G. Redefining outcome in an ongoing trial: convening a consensus panel. *Control Clin Trials* 1991;**12**:711–2.

Hemminki E. Study of information submitted by drug companies to licensing authorities. *BMJ* 1980; **280**:833–6.

Henderson WG, Moritz T, Goldman S, Copeland J, Sethi G. Use of cumulative meta-analysis in the design, monitoring, and final analysis of a clinical trial: a case study. *Control Clin Trials* 1995;**16**:331–41.

Hersh W, Price S. Identifying randomized controlled trials in conference proceedings abstracts. In *6th Annual Cochrane Colloquium Abstracts*. Baltimore; 1998.

Herxheimer A. Data on file cited in pharmaceutical advertisements: What are they? Presented at the International Congress on Biomedical Peer Review and Global Communications. Prague; 2001.

Hetherington J, Dickersin K, Chalmers I, Meinert CL. Retrospective and prospective identification of unpublished controlled trials: lessons from a survey of obstetricians and pediatricians. *Pediatrics* 1989; **84**:374–80.

Hewson S, Hannah M. Recruitment techniques in an ongoing trial. *Control Clin Trials* 1989;**10**:353.

Hewson S, Hannah M. P-14 outcome adjudication in an ongoing trial. *Control Clin Trials* 1990;**11**:283.

Higgins J, Soornroo M, Roberts I, Clarke M. Collecting unpublished data for systematic reviews: a proposal for a randomised trial. In *7th Annual Cochrane Colloquium. Abstracts*. Rome; 1999.

Hopewell S, Clarke M. How best to identify reports of randomized trials. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

Ioannidis JP, Cappelleri JC, Sacks HS, Lau J. The relationship between study design, results, and reporting of randomized clinical trials of HIV infection. *Control Clin Trials* 1997;**18**:431–44.

Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. *J Clin Epidemiol* 1999;**52**:281–91.

Jeng GT, Scott JR, Burmeister LF. A comparison of meta-analytic results using literature vs individual patient data. Paternal cell immunization for recurrent miscarriage [see comments]. *JAMA* 1995;**274**:830–6.

Kaufmann M. Luteinizing hormone-releasing hormone analogues in early breast cancer: updated status of ongoing clinical trials. *Br J Cancer* 1998;**78** Suppl 4:9–11.

Making clinical trialists register. *Lancet* 1991;**338**:244–5.

Laupacis A, Connolly SJ, Gent M, Roberts RS, Cairns J, Joyner C. How should results from completed studies influence ongoing clinical trials? The CAFA Study experience [see comments]. *Ann Intern Med* 1991; **115**:818–22.

Laupacis A. Results from clinical trials: how should they influence other ongoing clinical studies? [abstract]. *Control Clin Trials* 1991;**12**:635.

MacLean C, Morton S, Straus W, Ofman J, Roth E, Shekelle P. Unpublished data from United States Food and Drug Administration New Drug Application Reviews: how do they compare to published data when assessing nonsteroidal antiinflammatory drug (NSAm) associated dyspepsia? In *7th Annual Cochrane Colloquium Abstracts*. Rome; 1999.

Mallet S, Clarke M. A survey of the first 1000 Cochrane systematic reviews: use of unpublished data, subgroup analysis, authorship and number of trials included. *The Cochrane Methodology Register in The Cochrane Library*. Oxford: Update Software; 2001.

Mallet S, Hopewell S, Clarke M. The use of grey literature in the first 1000 Cochrane reviews. Presented at the 4th Symposium on Systematic Reviews: Pushing the Boundaries. Oxford; 2001.

Man-Son HM, Wells G, Lau A. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998;**13**:600–6.

Marsoni S, Liberati A, *et al*. When to stop an ongoing trial: the case of Adjuvant Chemotherapy on Colon

Cancer (ACCC) [abstract]. *Control Clin Trials* 1991; **12**:635.

McAreavey D, Exner DV, Curtin EL, Domanski MJ. beta-blockers in heart failure: recently completed and ongoing clinical trials [review] *Expert Opin Investig Drugs* 2000;**9**:415–28.

McAuley LM, Moher D, Tugwell P. The role of grey literature in meta-analysis. Presented at the International Congress on Biomedical Peer Review and Global communications. Prague; 2001.

McCormack KS. Are trials with individual patient data available different from trials without individual patient data available? The EU Hernia Trialists Collaboration. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

McDonald S. Improving access to the international coverage of reports of controlled trials in electronic databases: a search of the Australasian Medical Index. *Health Inf Libr J* 2002;**19**:14–20.

McMahon RP, Waclawiw MA, Geller NL, Barton FB, Terrin ML, Bonds DR. An extension of stochastic curtailment for incompletely reported and classified recurrent events: the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH). *Control Clin Trials* 1997; **18**:420–30.

Meinert CL. Toward prospective registration of clinical trials. *Control Clin Trials* 1988;**9**:1–5.

Meinert CL. Meta analysis: science or religion? *Control Clin Trials* 1989;**10**:257S–63S.

Mitchell RM. How useful is searching Biological Abstracts (BIOSIS) for reports of randomised trials? A comparison with MEDLINE and EMBASE in renal disease. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, *et al*. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2000; CD002096.

Neal B, MacMahon S. The World Health Organization–International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration: prospective collaborative overviews of major randomized trials of blood pressure-lowering treatments. *Curr Hypertens Rep* 1999;**1**:346–56.

Pater JL. Timing the collaborative analysis of three trials comparing 5-FU plus folinic acid (FUFA) to surgery alone in the management of resected colorectal cancer: a National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) perspective. *Stat Med* 1994; **13**:1337–40.

Pham B, Moher D, Platt R, McAuley L, Jones A, Klassen TP, *et al*. Detecting and adjusting for publication bias in meta-analysis: a systematic review. In *7th Annual Cochrane Colloquium Abstracts*. Rome; 1999.

Pignon JP, Arriagada R. Meta-analyses of randomized clinical trials: how to improve their quality? *Lung Cancer* 1994;**10** Suppl 1:S135–41.

Pocock SJ. Size of cancer clinical trials and stopping rules. *Br J Cancer* 1978;**38**:757–66.

Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996; **313**:1390–3.

Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. *JAMA* 1994;**272**:158–62.

Silagy CA. Developing a register of randomised controlled trials in primary care. *BMJ* 1993; **306**:897–900.

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

Simes RJ. Confronting publication bias: a cohort design for meta analysis. *Stat Med* 1987;**6**:11–29.

Simes RJ. Prospective meta-analysis of cholesterol-lowering studies: the Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) Collaboration. *Am J Cardiol* 1995;**76**:122C–6C.

Simes RJ, Greatorex V, Gebski VJ. Practical approaches to minimize problems with missing quality of life data. *Stat Med* 1998;**17**:725–37.

Singer J, Vandervoort M, Cairns J. Dealing with information during an ongoing trial. *Control Clin Trials* 1985;**6**:241.

Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997;**315**:640–5.

Sterne JAC, Bartlett CJ. Empirical evidence of bias? The hazard of ignoring heterogeneity in meta-epidemiology. In *9th Annual Cochrane Colloquium Abstracts*. Lyon; 2001.

Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med* 2002;**21**:1513–24.

Sterne JAC, Bartlett C, Jnni P, Egger M. Do we need comprehensive literature searches? A study of publication and language bias in meta-analyses of controlled trials. Presented at the 3rd Symposium on Systematic Reviews: Beyond the Basics. Oxford; 2000.

Stewart L, Tierney J. Publication bias is a serious threat to the validity of Cochrane Reviews. In *8th Annual Cochrane Colloquium Abstracts*. Cape Town; 2000.

Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**:418–22.

Sykes R. Being a modern pharmaceutical company: involves making information available on clinical trial programmes. *BMJ* 1998;**317**:1172.

The OSTR Collaborative Group. The Ottawa Stroke Trials Registry Collaborative Group and the development of the Ottawa Stroke Trials Registry (OSTR). *Control Clin Trials* 1994;**15**:503–11.

Verstraete M. Registry of prospective clinical trials – fifth report. *Thromb Haemost* 1982;**48**:334–8.

Wallace S, Daly C, Campbell M, Cody J, Grant A, Vale L, *et al*. After MEDLINE? Dividend from other potential sources of randomised controlled trials. Presented at the 2nd International Conference Scientific Basis of Health Services and 5th Annual Cochrane Colloquium. Amsterdam; 2001.

WHO International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure-lowering treatments. *J Hypertens* 1998;**16**:127–37.

Appendix 3

Data extraction form: ongoing trials in HTARs

Note: This is a simplified version.

Reviewer:	Date extracted:	NICE Guidance No:
Date Guidance Published:		HTA Report No:

Title: _____

Authors: _____

Expiry Date: _____

Intervention evaluated: _____

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

If drug, date licensed for use in UK: _____ Unknown; Not applicable

Patients/Participants: _____
Outcome measures: _____
No. of trials included: RCT ___; non-RCT ___ Cohort___; Case-series ___; Other___; Total___
How were the studies combined Descriptive; Meta-analysis; Other_____
HTAR main conclusions (effectiveness): _____
_____

Was the search of ongoing trials explicit: Yes, No/not sure
Was there an explicit search for unpublished data: Yes, No/not sure
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: _____ _____
_____ _____

Any relevant ongoing trials identified? No; Yes
If yes, number of ongoing trials _____

Reviewer's Comments _____

Note: the following items are only applicable if ongoing trials are identified.

Do the authors consider the impact of ongoing trials? Yes; No; Not sure
If yes, was the analysis? Narrative; Quantitative; Other _____
If quantitative, method(s) used: _____

If yes, what were the possible impact?
Internal validity Precision/power Generalisability
Different comparators Different patients Different settings
Variant intervention Different outcomes
Other_____

Do the ongoing trials impact on the HTAR conclusions? Yes; No; Not sure
If yes, more _____

Any research recommendations related to ongoing trials? Yes; No
If yes, more details: _____

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

Ongoing trials identified:

Trial	Trial stage	Why you think this is ongoing	Duration	Included in the TAR?	Intervention, comparator	Indications	Design	Source	Any interim results	What is its added value?

Appendix 4

Data extracted from the completed HTARs

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
4(15)	Apr 00	Mar 03	Third molar removal	Control	Impact 3rd molars	3	40	34	0	2	0	4	Narrat	0	0	1	1	1	2	0	1	0
4(17)	May 00	Mar 01	Paclitaxel or docetaxel alone or in combination with other drugs	Conventional chemotherapeutic regimes	Breast cancer and ovarian cancer	2–3	14	0	0	14	0	0	Narrat	0	0	1	0	2	2	0	1	1
4(23)	May 00	Apr 03	Stent	PTCA or CABG	Subacute IHD	2	34	0	0	34	0	0	Quant	0	0	1	14	26	40	0	0	1
4(18)	Jun 00	May 03	Liquid-based cytology	Control	Cervical screening test	3	48	3	0	0	9	36	Narrat	0	0	1	0	0	0	NA	NA	NA
4(26)	Sep 00	Sep 03	Implantable defibrillators	Conventional treatment (surgery, drugs, catheter ablation).	Cardiac arrythmias	1	8	1	0	7	0	0	Narrat	0	0	1	0	6	6	0	1	1
4(30)	Sep 00	Sep 01	Glycoprotein antagonists	Control, aspirin or heparin	Unstable angina	2	11	0	0	11	0	0	Narrat	0	0	1	3	2	5	0	1	0
4(33)	Oct 00	Oct 02	Combination therapy (interferon alpha and ribavirin)	Control; interferon alpha alone	Hepatitis C	1	21	2	0	19	0	0	Quant	1	0	1	0	16	16	0	0	0

continued

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
4(39)	Jul 00	Jun 03	PPI	Control	Gastrointestinal dyspepsia	2	11	0	0	11	0	0	Quant	1	1	1	0	0	0	NA	NA	NA
6(9)	Nov 00	Jun 02	Zanamivir	Control or other treatment for influenza	Influenza	1–2	11	0	0	11	0	0	Quant	1	0	1	0	8	8	1	1	0
5(11)	Dec 00	Nov 03	ACT	None	Hyaline cartilage defects	3	17	0	0	0	17	0	Narrat	0	0	1	0	10	10	0	1	1
5(1)	Jan 01	Dec 03	Donepezil, rivastigmine and galantamine	Control; donepezil, rivastigmine and galantamine; other forms of care, e.g. rehabilitation/specialist clinics	Alzheimer's disease	2	24	4	0	22	0	0	Narrat	1	0	1	0	19	19	0	1	1
5(2)	Jan 01	Jan 04	Riluzole	Control	Motor neurone disease	2	4	0	0	4	0	0	Quant	0	0	1	0	5	5	0	1	0
5(19)	Mar 01	Aug 02	Pioglitazone	Control; other anti-diabetic drugs.	Type 2 diabetes	1–2	14	0	0	14	0	0	Narrat	1	1	1	0	0	0	NA	NA	NA
5(18)	Mar 01	Feb 04	Orlistat (± other anti-obesity strategies)	Control; other anti-obesity pharmacological agent; other anti-obesity strategy	Overweight or obesity	?1–2	14	0	0	14	0	0	Quant	0	0	1	0	2	2	0	0	0

continued

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
5(13)	Apr 01	Mar 04	Temozolomide	Procarbazine (1 study). No comparator (6 studies)	Malignant glioma	1	7	0	0	1	1	0	Narrat	0	0	1	1	3	4	0	0	1
5(14)	Apr 01	Mar 04	Debriding agents	Other debriding agents; dressings	Surgical wounds	2	17	0	2	15	0	0	Narrat	0	0	1	0	0	0	NA	NA	NA
5(24)	May 01	Apr 04	Gemcitabine	Chemotherapeutic and/or immunotherapeutic drugs; surgery	Pancreatic cancer (all types)	2–3	71	0	0	7	57	7	Narrat	1	1	1	57	37	94	0	1	0
5(32)	Jun 01	May 03	Docetaxal; paclitaxal; gemcitabine; vinorelbine alone or in combination	Platinum-containing combination; older drug regimes; new drug regimes	Non-small-cell lung cancer	1	33	0	0	33	0	0	Narrat	1	1	1	0	0	0	NA	NA	NA
5(28)	Jul- 01	Jun 02	Topotecan used alone or in combination with other chemotherapeutic agents	Other chemotherapeutic agents	Ovarian cancer	2	2	0	0	2	0	0	Narrat	1	1	1	0	3	3	0	1	0

continued

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
6(2)	Sep 01	Aug 04	Fludarabine as second-line therapy	Control; other currently recommended treatment	B cell chronic lymphocytic leukaemia	1	9	0	0	2	7	0	Narrat	1	1	1	0	12	12	–	–	–
6(6)	Oct 01	Sep 04	Sibutramine	Control; other anti-obesity pharmacological agent; other anti-obesity strategy	Overweight or obese	?1–2	16	0	0	16	0	0	Quant	0	0	1	0	0	0	NA	NA	NA
4(9)	Nov 01	Nov 04	Azthioprine; beta interferon; cladribine; cyclophos-phamide; glatirimer; i.v. immuno-globulin; methotrexate; mitoxantrone	Control; other disease-modifying drug	Multiple sclerosis	2	22	2	0	20	0	0	Narrat	1	0	1	0	0	0	NA	NA	NA

continued

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
5(25)	Jan 02	Apr 05	Irinotecan, oxaliplatin, raltitrexed.	5-FU-based treatment; irinotecan; oxaliplatin or ralitrexed alone or in combination with other agents; non-chemotherapy-based palliative care	Colorectal cancer	1–2	24	0	0	24	0	0	Narrat	1	1	1	0	2	2	0	1	0
6(13)	Mar 02	Apr 05	Trastuzumab alone or in combination	Systemic therapy without trastuzumab	Breast cancer	2–3	4	0	0	2	2	0	Narrat	0	1	1	0	2	2	0	0	0
6(17)	Mar 02	Jan 05	Etanercept	Control; any other agent	Juvenile ideopathic arthritis	1	1	0	0	1	0	0	Narrat	0	0	1	0	0	0	NA	NA	NA
6(21)	Mar 02	Mar 05	Anti-TNFs (etanercept and or infliximab)	Control; any other agent	Rheumatoid arthritis	1	10	0	0	10	0	0	Quant	0	0	1	0	20	20	0	0	0
6(3)	Mar 02	Jan 05	Rituximab as third-line treatment	Control; any other recommended treatment	Follicular non-Hodgkin's lymphoma in relapse or chemoresistant	3	4	0	0	0	4	0	Narrat	1	1	1	0	4	4	1	0	1

continued

HTA No.	Publication date	Review date	Technology	Control	Disease	Authors' conclusions	Total studies	Reviews	Non-RCTs	RCTs	Cohort or case series	Other	Evidence synthesis	Explicitly search unpublished?	Explicitly search ongoing?	Grey literature or trial register searched?	Ongoing trials included	Ongoing trials not included	Total No. of ongoing trials	OT impact assessed?	Any impact on conclusion?	Any impact on FR recommended?
6(5)	Apr 02	Apr 05	Inhaler devices	Alternative inhaler device from list of included technologies	Asthma	2	58	1	20	37	0	0	Narrat	0	0	1	0	3	3	0	0	0
6(16)	Mar 02	Mar 05	Bupropion; NRT	Control; other pharmacological agents; other non-pharmacological agents	Smoking (cessation)	1	138	4	0	134	0	0	Quant	1	0	1	0	4	4	0	0	0
6(12)	Jul 02	Jun 05	Surgery	Control	Morbid obesity	2	18	0	0	17	1	0	Narrat	1	1	1	0	7	7	0	0	0
6(15)	Jun 02	Feb 05	MOM hip resurfacing	Control	Osteoarthritis	3	25	3	0	1	21	0	Narrat	0	0	1	0	0	0	NA	NA	NA
6(18)	May 02	Jun 05	Growth hormone	Control	5 indications for GH	1–2	33	0	11	22	0	0	Narrat	1	1	1	1	0	1	0	0	0

ACT, autologous cartilage transplantation; CABG, coronary artery bypass grafting; FR, future research; GH, growth hormone; IHD, ischaemic heart disease; MOM, metal-on-metal; NA, not applicable; Narrat, narrative; NRT, nicotine replacement therapy; OT, ongoing trials; PPI, proton pump inhibitor; PTCA, percutaneous transluminal coronary angioplasty; Quant, quantitative; TNF, tumour necrosis factor.

Appendix 5

Major sources of information on ongoing trials

Source	Description	Coverage	Sponsors	Access
General trial registers				
*Meta*Register (*m*RCT) www.controlled-trials.com/mrct	International database combining over 20 registers of ongoing trials in all areas of healthcare, to which contributors pay towards the cost of processing Some registers are no longer updated Website also allows access to the ISRCTN register of RCTs	International	Current Controlled Trials Ltd, UK-based sister company of BioMed Central	Public access with free registration
TrialsCentral.org http://www.trialscentral.org	A register of registers based at Center for Clinical Trials, Brown University, USA Provides links to registers which must be searched individually	International but mainly USA	Public and private groups, donations and honoraria	Free, public access
BioMed Central http://www.biomedcentral.com/	Offers the facility to publish trial protocols & trial results which are peer reviewed before publication	International	Independent publishing house	Free, public access
Medical Research Council (MRC) http://www.mrc.ac.uk/index/current-research/current-clinical_trials/	Provides information on solely MRC-supported and collaborative research MRC trials register links direct to *m*RCT	UK	Independent Government-funded body.	Free, public access
SEKNet http://www.seknet.co.uk	UK gateway to all Research Council (including MRC and ESRC) databases for information on research project activity and expertise	UK	Government-supported research councils. Developed and managed by Oakland Innovation Ltd	Free, public access
National Research Register (NRR) www.update-software.com/national www.nelh.nhs.uk	A register of ongoing and recently completed research projects funded by or of interest to the UK NHS Compiled from returns submitted by NHS trusts and other NHS organizations	UK	UK Department of Health	Free, public access
NHS Trusts Clinical Trials Register www.controlled-trials.com/mrct	A register of RCTs carried out in England for which the research costs have been met by the NHS	UK	Current Controlled Trials Ltd for NHS	Free, public access via the *m*RCT
ClinicalTrials.gov http://clinicaltrials.gov	Covers federally and privately supported clinical research in the USA and other countries, providing a means of linking patients with medical research	International but mainly USA and Canada	US National Institutes of Health with National Library of Medicine	Free, public access

continued

Source	Description	Coverage	Sponsors	Access
Centerwatch http://www.centerwatch.com/search.asp	Provides patients and clinicians with information about clinical research listing clinical trials being conducted internationally	International but mainly USA	Centerwatch, a publishing and information services company	Free, public access
Subject-specific trials registers				
Cancer.gov http://www.cancer.gov/cancerinfo/pdq/cancerdatabase	The National Cancer Institute's Cancer.gov site contains a wide range of information about clinical trials via the PDQ cancer information database. Also provides abstracts of clinical trial protocols	International	US National Cancer Institute, pharmaceutical industry and international groups	Free, public access
UK CCCR http://www.ctu.mrc.ac/ukcccr/text_only/search.html	A means of coordinating research relating to cancer in the UK including trials in cancer therapy	UK	Cancer Research Campaign, Imperial Cancer Research Fund and NHS R&D. Managed via Cancer Division of MRC	Free, public access
ICRP http://www.cancerportfolio.org/	Provides a classified summary of cancer research in the USA and the UK	International	Cancer-funding organizations in UK and USA	Free, public access
AIDSinfo (formerly ACTIS) http://www.aidsinfo.nih.gov	Provides access to wide-ranging resources on HIV/AIDS research, treatment and prevention for professionals and consumers, together with a database of HIV/AIDS clinical trials	USA	Several US federal agencies including NIH and HSRA	Free, public access
PsiTri http://www.psitri.helsinki.fi/	Bibliographic references and detailed information on clinical trials in mental health Compiled by several European universities and various mental health-related Cochrane Review Groups	International	The EC's QOL programme and the Finnish Ministry of Social Affairs and Health	Free, public access
Stroke Trials Directory http://www.strokecenter.org/trials/	A registry of clinical trials testing therapeutic interventions for stroke and cerebrovascular disease. Mainly directed at health professionals and researchers but also includes information for patients and families	International	Joint venture between International Stroke Center at Washington University of Medicine, American Stroke Association and National Institute of Neurological Disorders and Stroke	Free, public access

continued

Source	Description	Coverage	Sponsors	Access
Conference proceedings				
ISI proceedings http://wok.mimas.ac.uk/	Contains over 2.5 million records for more than 60,000 conferences from 1990 to 2002	International	ISI Web of Knowledge	Subscription
NLM Gateway http://gateway.nlm.nih.gov	Access to meeting abstracts, conference proceedings and the HSRProj database which provides access to ongoing grants and contracts in health services research	International	US National Library of Medicine	Free, public access
Medicalconferences.com http://www.medicalconferences.com	Information on over 7000 medical conferences and other events plus links to conference websites	International	Independent privately owned UK company	Free, public access
Zetoc http://zetoc.mimas.ac.uk/zetoc	Electronic Table of Contents of around 20,000 current journals and 16,000 conference proceedings published each year from 1993 to present	International	British Library	Free to use for members of JISC-sponsored UK higher and further education institutions. Also available to English NHS Regions and NHS Scotland
Information on drugs in development				
Pharmaprojects (and other similar commercial services provided by Adis Insight, etc.)	Global business intelligence service tracking drugs in R&D	International	PJB Publications Ltd, an independent publisher of international business news and information services for the pharmaceutical and other industries	Subscription
UK Medicines Information (UK Mi) http://www.ukmi.nhs.uk/	Access to information on new and unlicensed drugs.	UK	NHS pharmacy-based service	Mainly free, public access but also restricted access for NHS only
US Food and Drug Administration http://www.fda.gov	FDA website provides information on trials in progress.	USA	US Department of Health and Human Services	Free, public access
MEDLINEplus http://medlineplus.gov/	Access to searches of MEDLINE and ClinicalTrials.gov	USA	Information produced by the US National Library of Medicine and the National Institutes of Health	Free, public access

continued

Source	Description	Coverage	Sponsors	Access
Pharmaceutical industry http://ctr.glaxowellcome.co.uk	Some pharmaceutical companies have agreed to register clinical trials they have sponsored, e.g., Schering Health Care and GlaxoSmithKline)	UK	Drug companies	Free access but restricted to healthcare professionals and researchers
Internet				
Websites of professional organisations https://www.cmrteract.com/clintria http://www.asco.org	E.g. Association of British Pharmaceutical Industry and American Society of Clinical Oncology	International		Dependent on provider
Journals that publish trial protocols	E.g. *The Lancet*, *BioMed Central*	Various		Dependent on provider
Journal supplements	Some journals publish the abstracts of conferences in journal supplements	Various		Dependent on provider

Appendix 6

Completed evaluation form for trial registers

MetaRegister

Name of source:	MetaRegister of Controlled Trials (*m*RCT)
Location/url:	www.controlled-trials.com/mrct
Date of evaluation:	July 2003

General

Sponsors/Producers:	Current Controlled Trials Ltd which is part of Current Science Group which in turn is a sister company of BioMed Central
Type of info e.g. full protocol, abstract only, title only:	Varies according to the provider of the record
Diseases/interventions covered:	All
Multinational or national:	Multinational ☒ National ☐

Comments:

Accessibility e.g. password protected, public areas, identifiable via Internet search engines:

Free registration

Completed or ongoing trials	Completed ☐	Ongoing ☐	Both ☒
Proportion of trials in progress:	N/A		
Total no. of records in register:	Yes ☒	No ☐	

Specific info about trials

Study ID	Yes ☒	No ☐
ISRCTN	Yes ☒	No ☐
Title	Yes ☒	No ☐
Summary of purpose	Yes ☒	No ☐
Recruitment status	Yes ☒	No ☐
Study type & design	Yes ☒	No ☐

Comments: All studies should be RCTs. Extent of information dependent upon provider of record.

Sample size	Yes ☒	No ☐
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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 about the trial sponsor, name of organisation supplying the record and source of funding.

Information identification/retrieval

General layout appearance: Good

Ease of navigation: Good

Help feature Yes ☒ No ☐

Comments: Searching is intuitive. Has 'tips on searching' button. Inconsistency in requirement to enter registration details noted.

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: Can limit to searching specific registers, however, GlaxoSmithKline register is restricted to healthcare professionals and a separate registration must be obtained. Can order results by relevance, alphabetically or by register. Uses '!' as a 'sounds like' operator for words sounding the same but spelt differently e.g. US vs UK spelling. Allows 'quick' and 'advanced' search facilities.

Speed/response time: Good

Currency: Some providers are not currently maintaining the registers. These are shaded grey on the front screen. Current registers are blue.

Frequency of updating: Have a date when record was last reviewed and when the supplier processed the record.

Exporting facilities:

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

ISRCTN register

Name of source:	ISRCTN register
Location/url:	www.controlled-trials.com/
Date of evaluation:	July 2003

General		
Sponsors/Producers:	Current Controlled Trials Ltd which is part of Current Science Group which in turn is a sister company of BioMed Central	
Type of info e.g. full protocol, abstract only, title only:	Abstracts only	
Diseases/interventions covered:	All	
Multinational or national	Multinational ☒	National ☐
Comments:		

Accessibility e.g. password protected, public areas, identifiable via Internet search engines:

Free, public access

Completed or ongoing trials	Completed ☐	Ongoing ☐	Both ☒
Proportion of trials in progress:	N/A		
Total no. of records in register:	Yes ☒	No ☐	

Specific info about trials		
Study ID	Yes ☒	No ☐
ISRCTN	Yes ☒	No ☐
Title	Yes ☒	No ☐
Summary of purpose	Yes ☐	No ☒
Recruitment status	Yes ☐	No ☒
Study type & design	Yes ☒	No ☐
Comments: All studies should be RCTs. Gives date that the ISRCT was assigned		
Sample size	Yes ☐	No ☒
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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 given

Information identification/retrieval

General layout appearance: Good

Ease of navigation: Good

Help feature Yes ☒ No ☐

Comments: 'Tips on searching' gives detailed search help

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:

Speed/response time: Good

Currency: Only gives date when ISRCTN has been allocated

Frequency of updating: As above

Exporting facilities:

Mark records Yes ☐ No ☒

Record format Yes ☐ No ☒

Download to disc Yes ☐ No ☒

Email Yes ☐ No ☒

Print Yes ☒ No ☐

UK National Research Register

Name of source: National Research Register

Location/url: www.update-software.com Also available via National Electronic Library for Health: www.nelh.nh.uk

Date of evaluation: July 2003

General

Sponsors/Producers: Sponsored by the UK Department of Health. Produced by Update Software.

Type of info e.g. full protocol, abstract only, title only:	Abstract only	
Diseases/interventions covered:	All	
Multinational or national	Multinational ☐	National ☒
Comments:	Data are submitted mostly from organisations within the UK NHS, however, includes international studies where a study site is in the UK	
Accessibility e.g. password protected, public areas, identifiable via Internet search engines:		
Free public access.		
Completed or ongoing trials	Completed ☐	Ongoing ☐ Both ☒
Proportion of trials in progress:	N/A	
Total no. of records in register:	Yes ☒	No ☐
Specific info about trials		
Study ID	Yes ☒	No ☐
ISRCTN	Yes ☒	No ☐
Title	Yes ☒	No ☐
Summary of purpose	Yes ☒	No ☐
Recruitment status	Yes ☒	No ☐
Study type & design	Yes ☒	No ☐
Comments:		
Sample size	Yes ☒	No ☐
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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:	Contact details of investigators given	
Information identification/retrieval		
General layout appearance:	Good. However, appearance of multi-registers is cumbersome	
Ease of navigation:	Good. Need to browse and display results from each register separately. Advantage in being able to display search history.	
Help feature	Yes ☒	No ☐
Comments:	Extensive help feature on searching/information retrieval.	
Links to other sources	Yes ☒	No ☐

Comments: Links to NHS R&D pages and list of funding sources.

Search facilities:

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

Comments: Can limit by date of publication; field; new items added to the current issue and updated items in the current issue. The 'export' button does not function

Speed/response time: Good

Currency: NRR is issued quarterly, however, no indication about how current the individual records are.

Frequency of updating: Data are submitted by provider organisations and it is their responsibility to keep their 'returns' up-to-date. Deletion of records is not automatic, therefore, no records are removed until data provider informs the NRR

Exporting facilities:

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

Cancer.gov

Name of source: Cancer.gov

Location/url: www.cancer.gov/search/clinical_trials

Date of evaluation: August 2003

General

Sponsors/Producers: National Cancer Institute

Type of info e.g. full protocol, abstract only, title only: Abstracts. Patients and health professional versions. Patient version: title, basic study info, study lead organisation, study size & contacts Health professional version: as above plus objectives, entry criteria, projected accrual, outline, published results

Diseases/interventions covered: Cancer

Multinational or national: Multinational ☒ National ☐

Comments:

Accessibility e.g. password protected, public areas, identifiable via Internet search engines:

Free, public access

Completed or ongoing trials	Completed ☐	Ongoing ☐	Both ☒
Proportion of trials in progress:	Yes		
Total no. of records in register:	Yes ☒	No ☐	

Specific info about trials

Study ID	Yes ☒	No ☐
ISRCTN	Yes ☐	No ☒
Title	Yes ☒	No ☐
Summary of purpose	Yes ☒	No ☐
Recruitment status	Yes ☒	No ☐
Study type & design	Yes ☒	No ☐

Comments: Fuller information given in 'advanced' mode

Sample size	Yes ☒	No ☐
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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: the study sites	Includes study investigators and lead organisation, with locations of	

Information identification/retrieval

General layout appearance:	Excellent	
Ease of navigation:	Excellent	
Help feature	Yes ☒	No ☐

Comments: Also gives on-line help. Basic and advanced search facilities

Links to other sources	Yes ☒	No ☐

Comments: These are located on Cancer.gov website

Search facilities:

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

Limits	Yes ☐	No ☒

Comments: Must use either basic or advanced 'forms'. Searches can be refined by linking to 'advanced' form.

Speed/response time:	Excellent
Currency:	Gives date of latest modification of the document
Frequency of updating:	N/A. States 'updated frequently'

Exporting facilities:		
Mark records	Yes ☒	No ☐
Record format	Yes ☐	No ☒
Download to disc	Yes ☒	No ☐
Email	Yes ☐	No ☒
Print	Yes ☒	No ☐

ClinicalTrials.com

Name of source:	ClinicalTrials.com
Location/url:	http:clinicalTrials.gov
Date of evaluation:	August 2003

General

Sponsors/Producers:	A US federally sponsored National Institutes of Health database, developed by the US National Library of Medicine
Type of info e.g. full protocol, abstract only, title only:	Very comprehensive summaries
Diseases/interventions covered:	All

Multinational or national	Multinational ☒	National ☐

Comments: Includes mainly studies carried out in the USA and Canada

Accessibility e.g. password protected, public areas, identifiable via Internet search engines:

Free, public access

Completed or ongoing trials	Completed ☐	Ongoing ☐	Both ☐
Proportion of trials in progress:	N/A		
Total no. of records in register:	Yes ☒	No ☐	

Specific info about trials

Study ID	Yes ☒	No ☐
ISRCTN	Yes ☐	No ☒

Title	Yes ☒	No ☐
Summary of purpose	Yes ☒	No ☐
Recruitment status	Yes ☒	No ☐
Study type & design	Yes ☒	No ☐
Comments:		
Sample size	Yes ☒	No ☐
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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:	Sponsor, location and contact information given	

Information identification/retrieval

General layout appearance:	Good	
Ease of navigation:	Good	
Help feature	Yes ☒	No ☐
Comments:		
Links to other sources	Yes ☒	No ☐
Comments:		
Search facilities:	Yes ☒	No ☐
Keywords	Yes ☒	No ☐
Index terms	Yes ☒	No ☐
Phrases	Yes ☒	No ☐
Boolean	Yes ☒	No ☐
Truncation	Yes ☐	No ☒
Limits	Yes ☒	No ☐
Comments:	Basic search: Can enter words or phrases.	
	Focused search: Can search on disease; treatment; location of trial; additional terms; age group; study phase; sponsor; study ID etc.	
	Browse facility: By condition from an alphabetical list or by sponsor. Will automatically add synonyms to searches.	
Full text	Yes ☐	No ☒
Speed/response time:	Good	
Currency:		

Frequency of updating:	Gives date of when a record was last reviewed and when the record was processed by ClinicalTrials.com

Exporting facilities:

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

Centerwatch

Name of source:	Centerwatch
Location/url:	www.centerwatch.com/
Date of evaluation:	August 2003

General

Sponsors/Producers:	Centerwatch, a US publishing and information company
Type of info e.g. full protocol, abstract only, title only:	'One line' summaries designed to recruit potential participants to trials
Diseases/interventions covered:	All

Multinational or national Multinational ☒ National ☐

Comments:

Accessibility e.g. password protected, public areas, identifiable via Internet search engines:

Free, public access.

Completed or ongoing trials	Completed ☐	Ongoing ☒	Both ☐
Proportion of trials in progress:	Yes		
Total no. of records in register:	Yes ☒	No ☐	

Specific info about trials

Study ID	Yes ☒	No ☐
ISRCTN	Yes ☐	No ☒
Title	Yes ☐	No ☒
Summary of purpose	Yes ☒	No ☐
Recruitment status	Yes ☒	No ☐
Study type & design	Yes ☐	No ☒

Comments: Only summary information given, designed to recruit potential participants. Wide variation in amount of information given

Sample size	Yes ☒	No ☐
Patient incl/excl criteria	Yes ☒	No ☐
Study start/end date	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 provided	

Information identification/retrieval

General layout appearance:	Good	
Ease of navigation:	Good	
Help feature	Yes ☒	No ☐
Comments:		
Links to other sources	Yes ☒	No ☐
Comments:	Links to international trials	

Search facilities:

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

Comments: Quick or advanced modes. Allows searches by medical condition and/or location

Full text	Yes ☐	No ☒
Speed/response time:	Good	
Currency:	N/A	
Frequency of updating:	N/A	

Exporting facilities:

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

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We look forward to hearing from you.

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