Chapter 19: Prospective meta-analysis

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Key points

- A prospective meta-analysis is a meta-analysis of studies (usually randomized trials) that were identified, evaluated and determined to be eligible for the meta-analysis before the results of any of those studies became known.
- Prospective meta-analyses enable hypotheses to be specified in advance of the results of individual trials; enable prospective application of study selection criteria; and enable *a priori* statements of intended analyses. As meta-analyses rather than multi-centre trials, they allow variation in the protocols of the included studies, while maximizing power in the pre-planned meta-analyses.
- Prospective meta-analyses are usually undertaken by a collaborative group, and they usually collect and analyse individual patient data.
- Protocols are important for prospective meta-analyses, and they may be published as protocols for Cochrane reviews. The Cochrane Prospective Meta-analysis Methods Group maintains a registry of prospective meta-analysis projects and is able to provide advice on their conduct.

19.1 Introduction

19.1.1 What is a prospective meta-analysis?

A properly conducted systematic review defines the question to be addressed in advance of the identification of potentially eligible trials. Systematic reviews are by nature, however, retrospective because the trials included are usually identified after the trials have been completed and the results reported (Pogue 1998, Zanchetti 1998). Knowledge of the results of individual randomized trials may introduce bias into a retrospective systematic review if the selection of the key components of the review question is based on reports of one or more positive trials. This might include influencing:

- the criteria for study selection (i.e. the types of trial considered eligible);

- the selection of the target population;
- the nature of the intervention;
- the choice of comparator; and
- the outcomes to be assessed and their measures.

Take, for example, a systematic review in which the results of one study are in the opposite direction to those of the other studies in the review. The authors of the review discuss possible explanations for this apparent heterogeneity and decide that there is a clinical explanation. On this basis, the authors subsequently decide to exclude the study. This may be a reasonable decision; however, it is one made after the effect of the study's results on the overall summary estimate is known, and hence is intrinsically problematic.

As described in detail in Chapter 10 (Section 10.2), awareness of the results of a trial may also influence the decision to publish those results. Even within a published trial, results may be selectively reported, thereby introducing a more subtle form of publication bias into the review (Chan 2004).

A prospective meta-analysis (PMA) is a meta-analysis of studies (usually randomized trials) that were identified, evaluated and determined to be eligible for the meta-analysis before the results of any of those studies became known. They have features in common with both cumulative meta-analyses and those involving individual patient data (Egger 1997). PMA can help to overcome some of the recognized problems of retrospective meta-analyses (see also Chapter 18, Section 18.5) by:

- enabling hypotheses to be specified a priori ignorant of the results of individual trials;
- enabling prospective application of study selection criteria; and
- enabling *a priori* statements of intended analyses, including subgroup analyses, to be made before the results of individual trials are known. This avoids potential difficulties in interpretation related to the data-dependent emphasis on particular subgroups.

Systematic reviews also depend on the ability of the review authors to obtain data on all randomized patients for the relevant outcomes, which can be difficult if full information is not reported in the trial publications. As most PMAs will collect and analyse individual patient data (IPD) they will be able to overcome this problem, with the additional advantage of being able to conduct time-to-event analyses if appropriate. Planned subgroup analyses based on patient-level factors can give misleading results if relying only on aggregate-level data, highlighting another advantage of IPD. PMA also provides a unique opportunity for trial design, data collection and other clinical trial processes to be standardized across trials. For example, the investigators may agree to use the same instrument to measure a particular outcome, and to measure the outcome at the same time-points in each trial. In a Cochrane review of interventions for preventing obesity in children, for example, the heterogeneity and unreliability of the some of the outcome measures made it difficult to pool data across trials (Summerbell 2005). A prospective meta-analysis of this question has proposed a set of commonly shared standards, so that some of the issues raised by lack of standardization can be addressed (Steinbeck 2006).

19.1.2 What is the difference between a prospective meta-analysis and a large multi-centre trial?

Prospective meta-analyses are an attractive option to clinical trialists who, although appreciating the benefits of single, adequately sized trials, are unable to undertake them (Simes 1987, Probstfield 1998). It can be a useful methodology, for example, when large sample sizes are required to ensure adequate power, but single, large-scale trials are not feasible. This could be due to local interests

preventing participation in a trial when information is perceived to be ‘lost overseas’. This can also be a particular problem in rare diseases where gaining access to large numbers of trial participants in a timely manner may be difficult.

Hence, an alternative is for investigators to conduct their own study locally, and to collaborate with the investigators of similar studies, arranging for the results to be combined at the completion of each trial. This enables individual investigators to maintain a certain amount of autonomy, and at the same time to plan appropriately for the meta-analysis. Another situation where it may be beneficial, particularly in the absence of mandatory prospective registration of randomized trials, is when two or more trials addressing the same question commence and the investigators are ignorant of the existence of the other trial(s). Once similar trials are identified, investigators can collaborate (adapting data collection if necessary) and plan prospectively to combine their results in a meta-analysis.

What also distinguishes a PMA from a multicentre trial is that there is no requirement in a PMA for the protocols to be identical across studies. Variety in the design of the studies may be viewed by some as a desirable feature of PMA, and thus a degree of expected variation in populations or in aspects of the interventions is considered acceptable. FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) is an example of a pre-planned meta-analysis of eight studies of exercise-based interventions in a frail elderly population (Schechtman 2001). The eight FICSIT sites defined their own interventions using site-specific endpoints and evaluations and differing entry criteria (except that all participants were elderly). This deliberate introduction of *systematic* variability in design, known as a ‘meta-experimental design’, is a possible approach to PMA (Cholesterol Treatment Trialists' (CTT) Collaborators 2005).

19.1.3 What healthcare areas have used the prospective meta-analysis approach?

Prospective meta-analysis is a method that has been utilized in recent years by trialists in cardiovascular disease (Simes 1995, WHO - ISI Blood Pressure Lowering Treatment Trialists' Collaboration 1998), childhood leukaemia (Shuster 1996, Valsecchi 1996) and childhood and adolescent obesity (Steinbeck 2006). In addition, some have identified areas, such as infectious diseases, where the opportunity to use PMA has largely been missed (Ioannidis 1999). The Cochrane Prospective Meta-analysis Methods Group web site includes a list of ongoing and completed PMA where further information can be found (Ghersi 2005).

19.1.4 What resources do I need?

PMAs are significant undertakings and should not be embarked on lightly. They are likely to take many years to complete and require a committed, ongoing, appropriately staffed and adequately funded Secretariat. Once the PMA collaborative group is formed (see Section 19.2) resources are needed to ensure the ongoing commitment of the group over many years, usually a much longer time period than is required for a retrospective IPD review (see Chapter 18). The Secretariat will be required to organize regular teleconferences, face-to-face meetings (at least annually), newsletters, update contact details and implement other mechanisms to keep the collaborative group together. This type of activity is akin to that undertaken by the co-ordinating centre of a multicentre randomized trial. A benefit of these Secretariat activities is that they often help facilitate adherence to the PMA protocol and encourage complete follow-up within individual participating trials.

19.2 The collaborative nature of prospective meta-analyses

19.2.1 Collaborative groups

As with IPD meta-analyses (see Chapter 18, Section 18.2.1) most PMA are carried out and published by collaborative groups. The collaborative group should include representatives from each of the participating trials and will usually have a steering group or Secretariat who manages the project on a day-to-day basis. The collaborative group may choose to create small, *ad hoc* groups to address specific issues as they arise, and to provide advice to the steering group or secretariat on clinical, technical or other issues that may impact on the project.

19.2.2 Negotiating collaboration

As with IPD meta-analyses (see Chapter 18, Section 18.2.2) negotiating and establishing a strong collaboration with the participating trialists is essential for the success of a PMA. The focus of a PMA, however, is not primarily about locating and obtaining data from individual trials. As the collaboration needs to be formed prior to the results of any trial being known, the focus of a PMA's collaborative efforts, at least initially, is on reaching agreement regarding study population, design and data collection methods for each of the participating studies. When members of a PMA collaborative group agree to participate in the project, they need to agree to a core common protocol and core common data items that will be collected across all trials. Individual trials can include local protocol amendments or additional data items but they need to ensure that these will not compromise the core common protocol elements.

In a PMA, efforts are made to identify *all* ongoing trials, both to maximize precision and to avoid bias that might be introduced by excluding studies based (at least in part) on knowledge of the results of those studies. To certify that an individual study is eligible for inclusion in the PMA there should be evidence to support the claim that, at the time of the agreement to be part of the PMA, trial results were not known outside the trial's own data monitoring committee. This should ideally be in the form of evidence that the trial was prospectively registered (Laine 2007). It is also advisable for the collaborative group to obtain an explicit (and signed) agreement from each of the trial groups to collaborate. The idea is to encourage substantive contributions by the individual investigators and to get 'buy-in' to the concept of the PMA and the details of the protocol.

19.2.3 Confidentiality

Confidentiality issues regarding data anonymity and security are similar to those described for IPD meta-analyses in Chapter 18 (Section 18.2.3). Specific issues for PMA include adequate planning regarding how to deal with trials within the PMA that reach completion and will publish their results, and how to manage issues relating to data and safety monitoring, including the impact of interim analyses of individual trials in the PMA, or possibly a pooled interim analysis of the PMA (see also Section 19.5.2).

19.3 The prospective meta-analysis protocol

19.3.1 What should the protocol contain?

All PMAs should have a publicly available protocol. Developing a protocol for a PMA is similar, conceptually, to doing so for a single trial. The essential elements of a PMA are detailed as follows and summarized in Box 19.3.a.

Objectives, eligibility and outcomes

As in any protocol, the first important step is to define the hypotheses and then to establish eligibility criteria for studies. For example, studies to be included in the PMA may be required to use random assignment of participants to interventions, although it is possible to include other study designs in a PMA. If randomized, the individual trials may choose to share a common randomization method, or at least to use the same stratification factors. The required attributes of the participating population need to be specified, as do the minimum requirements for each of the interventions and the comparator arms. The protocol should also specify what outcomes need to be measured, when and how they should be measured, which are primary and which are secondary, as well as other features of study design as necessary. If a PMA is established de novo, it may be possible for each trial in the PMA to share exactly the same trial protocol.

Search methods

The protocol should describe in detail the efforts made to identify ongoing trials, including how potential collaborators have been (or will be) located and approached to participate.

Trial details

Details of trials already identified for inclusion (if relevant) should be listed in the protocol. The listing might include the anticipated number of participants and timelines for each participating trial. The protocol should include a statement outlining if, at the time of submission for registration, any trial results were known (to anyone outside the trial's own data monitoring committee). Trials should be included only if their results were unknown at the time they were identified and added to the PMA. If eligible trials are identified but not included in the PMA because their results are already known, the PMA protocol should outline how these data will be dealt with. For example, secondary sensitivity analyses using aggregate or individual patient data from these trials might be undertaken. The protocol should describe actions to be taken if subsequent trials are located while the PMA is in progress.

Analysis plan

The protocol should outline the plans for the collection and analyses of data in a similar manner to that of an IPD meta-analyses (see Chapter 18). This would include details of sample size and power calculation (for the PMA), any interim analyses to be undertaken, and details of planned subgroup analyses. Strategies for addressing additional questions beyond the main hypothesis of interest can also be incorporated in a PMA. These additional questions can be added as long as the results of studies to be included in the analysis are not known, i.e. they not ‘data-driven’ research questions. Of note, there may be analyses that are unique to the PMA, that are *not* done within the individual trials, such as subgroup analyses.

The investigators of trials to be included in a PMA should generally be asked to agree to provide individual patient data. The protocol should describe what will occur if the investigators of some studies within the PMA are unable (or unwilling) to provide patient-level data, perhaps because of concerns about confidentiality or informed consent. Would the PMA Secretariat, for example, accept appropriate summary data? (A two-stage analysis could be performed, in which the effect estimate of interest is calculated separately within each study, using the patient-level data, and those within-study estimates are then combined across studies using standard meta-analytic methods.) The protocol should specify whether it is intended to update the PMA data at regular intervals via ongoing cycles of data collection (e.g. 5 yearly), and hence when trialists would be expected to supply updated, long-term outcome data.

Management and co-ordination

The PMA protocol should outline details of project management structure (including any committees, see Section 19.2.1), the procedures for data management (how data are to be collected, the format required, when data will be required to be submitted, quality assurance procedures, etc; see Chapter 18, Section 18.3), and who will be responsible for the statistical analyses.

Publication policy

A key element of the PMA protocol is the publication policy. It is essential to have a policy regarding authorship (e.g. specifying that publication will be in the group name, but also include a list of individual authors). A policy regarding manuscript preparation is also important. For example, it might be specified that drafts of papers be circulated to all trialists for comment, prior to submission for publication. There might be a writing committee, like those that are often formed within cooperative study groups.

A unique issue that arises in the context of the PMA (which would generally not arise for a multicentre study or an IPD meta-analysis) is whether or not individual studies should publish on their own and the timing of those publications. Most investigators would want to publish their own studies individually in addition to contributing to the PMA, and it is likely that the investigators would want these publications to appear before the PMA is published, so as to avoid issues related to duplicate publication of the same data. In a similar spirit, though, any PMA publication(s) should clearly indicate the sources of the included data and refer to prior publications of the same data. The PMA protocol should also state what will occur if any of the participating trials fail to publish their individual results within a specified timeframe. This may occur if a trial is not completed due to insufficient funds, is terminated prematurely or the trial simply remains unpublished after a pre-specified date. The protocol should also address how to deal with trials that renege on their agreement to participate in the PMA.

Box 19.3.a: Elements of a prospective meta-analysis protocol

Objectives:

- Define the specific hypotheses/objectives.

Methods: Criteria for considering studies for this review:

- Eligibility criteria for trial design (e.g. requirements for randomization, minimum follow-up).
- Eligibility criteria for the patient population.
- Eligibility criteria for each intervention and comparator.
- Outcomes information: specification of primary and secondary endpoints, definitions, measurement instruments, timing.
- Details of subgroups.

Methods: Search methods for identification of studies:

- Describe efforts made to identify ongoing trials.

Methods: Data collection and analysis:

- Trial details:
  - List details of trials identified for inclusion.
  - A statement outlining if, at the time of submission for registration of the PMA, any trial results were known (to anyone outside the trial's own data monitoring committee). Trials should be included only if their results were unknown at the time

they were identified and added to the PMA.

- Whether a signed agreement to collaborate has been obtained from the appropriate representative of each trial (e.g. the Sponsor or Principal Investigator).

- Analysis Plan:
  - Details of sample size and power calculation (for the PMA), interim analyses, subgroup analyses etc.
- Management and Coordination:
  - Details of management structure and committees.
  - Data management (data to be collected, format required, when required, quality assurance procedures, etc).
  - Responsibility for statistical analyses.
- Publication Policy:
  - Policy regarding authorship (e.g. publication in 'group' name).
  - Writing Committee (membership, responsibilities).
  - Policy regarding manuscript (e.g. circulated to all trialists for comment).

19.3.2 Publication of the protocol

If prepared as a Cochrane review, the PMA protocol should be submitted to the appropriate Cochrane Review Group to appear in the *Cochrane Database of Systematic Reviews*. Otherwise, a protocol should be published elsewhere (for example, the CTT/PPP Protocol (Cholesterol Treatment Trialists' (CTT) Collaborators 2005)). It is also desirable that PMA projects are registered on the Cochrane Prospective Meta-analysis Methods Group web site (see Box 19.6.a) and information about the project should be updated at least annually. Each trial within the PMA should be registered on a publicly accessible, WHO recognized, Primary Registry (www.who.int/ictrp/network/list_registers) prior to enrolment of the first participant, in accordance with international requirements (Sim 2006, Laine 2007).

19.4 Data collection in prospective meta-analysis

Participating trials in a PMA usually supply individual patient data once their individual trial is completed and published. The advantage of the PMA design is that trialists prospectively decide what data they will collect and in what format, making the need to redefine and recode supplied data less problematic than is often the case with a retrospective IPD. The PMA should develop a data transfer protocol that may incorporate current data interchange standards, such as those developed by the Clinical Data Interchange Standard Consortium (CDISC; www.cdisc.org).

Once data are received by the PMA Secretariat, they should be rigorously checked using the same procedures as for IPD meta-analyses, including checking for missing or duplicated data, running data plausibility checks, assessing patterns of randomization and ensuring the information supplied is up to date (see Chapter 18, Section 18.4.4). Data queries will be resolved by direct consultation with the individual trialists before being included in the final dataset for analysis.

19.5 Analysis issues in prospective meta-analysis

19.5.1 General approach

Most PMAs will use similar general analysis techniques to that of retrospective IPD meta-analyses. These techniques are outlined in detail in Chapter 18 (Section 18.4) and include the general approach to these analyses and the ability to undertake time-to-event analyses (if appropriate). The use of patient-level data also permits more statistically powerful subgroup analyses and multilevel modelling to explore associations between intervention effects and patient characteristics, as well as prognostic modelling in some cases. Chapter 18 (Section 18.4.7) describes some of the potential software packages that can be used to analyse these types of data.

19.5.2 Interim analysis and data monitoring

It is increasingly common practice for individual clinical trials to include a plan for interim analyses of the data, and to monitor safety. PMA offers a unique opportunity to perform these interim looks using the data contributed by all trials. The data may be pooled for this analysis, or looked at separately for each trial and the results then shared amongst the data monitoring committees of the participating trials.

The ability to perform interim analyses raises a number of ethical issues. Is it, for example, appropriate to continue randomization to ongoing studies after an overall benefit (in terms of the primary outcome, for example) of an intervention has been demonstrated? When results are not known in the subgroups of clinical interest, or for less common endpoints, should the investigators proceed with the study to obtain further information on overall net clinical benefit, for example, evidence of benefit for one outcome but not another, or evidence of harm.

If each trial has its own data monitoring committee, then communication among committees might be beneficial in this regard, as recommended by Hillman and Louis (Hillman 2003). The various committees would need to be aware of the other trials included within the PMA and their results, because these external considerations might influence the decisions made by a given monitoring committee: for example, whether or not to close a study early because of evidence of efficacy. Conversely, it might be argued that knowledge of emerging safety data from all participating trials might reduce the chances of spurious early stopping of an individual trial due to concerns about interim safety outcomes. It would be helpful, thus, for the various trial data safety monitoring committees to adopt a common understanding that individual trials should not be stopped until the goals of the PMA, with respect to subgroups and uncommon endpoints (or ‘net clinical benefit’), are achieved.

Another possible option might be to consider limiting enrolment in the continuing trials to patients in the subgroup(s) of interest if such a decision makes clinical and statistical sense. In any case, it might be appropriate to apply the concepts of sequential clinical trials methodology, such as the approach described by Whitehead (Whitehead 1997), to derive rigorous and stringent stopping rules for the PMA as individual trial results become available.

19.6 Chapter information

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Box 19.6.a: The Cochrane Prospective Meta-analysis Methods Group

The role of the Prospective Meta-analysis Methods Group (PMA MG) is:

- To provide a mechanism to enable the registration of prospective meta-analyses:
    - cochrane (via Cochrane Review Groups); and
    - non-Cochrane (via PMA MG);
- To provide a mechanism for evaluating protocols submitted for registration to ensure they are indeed prospective meta-analyses. This may be achieved by:
    - providing training for members of Cochrane Review Groups (e.g. editors and peer-reviewers);
    - members of the PMA MG peer reviewing protocols; and
    - a checklist for investigators performing or peer-reviewing a PMA;
- To develop appropriate methodological standards for prospective meta-analyses.
- To provide advice and support to those embarking on (or contemplating) prospective meta-analyses.

Membership of the group is open to anyone who is conducting, has conducted, or is interested in conducting a prospective meta-analysis, regardless of the area of health care investigated. To join, individuals are asked to detail their level of commitment on a Prospective Meta-analysis Methods Group Questionnaire (available on the PMA web site, below). Members will be asked to update this information annually.

Web site: www.cochrane.org/docs/pma.htm

19.7 References

Chan 2004
Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004; 291: 2457-2465.

Cholesterol Treatment Trialists' (CTT) Collaborators 2005
Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet* 2005; 366: 1267-1278.

Egger 1997
Egger M, Davey Smith G. Meta-analysis: potentials and promise. *BMJ* 1997; 315: 1371-1374.

Ghersi 2005
Ghersi D. Cochrane Prospective Meta-analysis Methods Group. *About the Cochrane Collaboration (Methods Groups)* 2005, Issue 2. Art No: CE000132.

Hillman 2003
Hillman DW, Louis TA. DSMB case study: decision making when a similar clinical trial is stopped early. *Controlled Clinical Trials* 2003; 24: 85-91.

Ioannidis 1999
Ioannidis JPA, Lau J. State of the evidence: current status and prospects of meta-analysis in infectious diseases. *Clinical Infectious Diseases* 1999; 29: 1178-1185.

Laine 2007
Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, Haug C, Hebert PC, Kotzin S, Marusic A, Sahni P, Schroeder TV, Sox HC, Van der Weyden MB, Verheugt FW. Clinical trial registration: looking back and moving ahead. *Canadian Medical Association Journal* 2007; 177: 57-58.

Pogue 1998
Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomissed controlled trials. *The Lancet* 1998; 351: 47-52.

Probstfield 1998
Probstfield J, Applegate WB. Prospective meta-analysis: Ahoy! A clinical trial? *Journal of the American Geriatrics Society* 1988; 43: 452-453.

Schechtman 2001
Schechtman K, Ory M. The effects of exercise on the quality of life of frail older adults: a preplanned meta-analysis of the FICSIT trials. *Annals of Behavioural Medicine* 2001; 23: 186-197.

Shuster 1996
Shuster JJ, Gieser PW. Meta-analysis and prospective meta-analysis in childhood leukemia clinical research. *Annals of Oncology* 1996; 7: 1009-1014.

Sim 2006
Sim I, Chan AW, Gulmezoglu M, Evans T, Pang T. Clinical trial registration: transparency is the watchword. *The Lancet* 2006; 367: 1631-1633.

Simes 1987
Simes RJ. Confronting publication bias: a cohort design for meta-analysis. *Statistics in Medicine* 1987; 6: 11-29.

Simes 1995
Simes RJ. Prospective meta-analysis of cholesterol-lowering studies: the Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists' (CTT) Collaboration. *American Journal of Cardiology* 1995; 76: 122c-126c.

Steinbeck 2006
Steinbeck KS, Baur LA, Morris AM, Ghersi D. A proposed protocol for the development of a register of trials of weight management of childhood overweight and obesity. *International Journal of Obesity* 2006; 30: 2-5.

Summerbell 2005
Summerbell CD, Waters E, Edmunds LD, Kelly S, Brown T, Campbell KJ. Interventions for preventing obesity in children. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art No: CD001871.

Valsecchi 1996
Valsecchi MG, Masera G. A new challenge in clinical research in childhood ALL: the prospective meta-analysis strategy for intergroup collaboration. *Annals of Oncology* 1996; 7: 1005-1008.

Whitehead 1997
Whitehead A. A prospectively planned cumulative meta-analysis applied to a series of concurrent clinical trials. *Statistics in Medicine* 1997; 16: 2901-2913.

WHO - ISI Blood Pressure Lowering Treatment Trialists' Collaboration 1998
WHO - ISI Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomised trials of blood-pressure-lowering treatments. *Journal of Hypertension* 1998; 16: 127-137.

Zanchetti 1998
Zanchetti A, Mancia G. Searching for information from unreported trials - amnesty for the past and prospective meta-analysis for the future. *Journal of Hypertension* 1998; 16: 125.