Data monitoring (and safety) committees – what are they and why do we need them?

Primary Care Alliance for Clinical Trials (PACT) Network

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Ethics and randomised controlled trials

Randomised controlled trials (RCTs) are considered the gold standard of evidence for clinical decisions and are the keystone of the Cochrane Collaboration. However, such trials are resource intensive in terms of time and money, difficult to conduct, and usually rely on the altruism of the population for their participants.

It is therefore essential that ethical principles underpin RCTs. Two important principles are: first, do no harm, and second, that a genuine state of clinical equipoise, or uncertainty, should exist about the treatments being investigated.[1,2] Although these conditions may be met at the commencement of a trial, the situation may change once results from trial participants accrue.

The purpose of data monitoring committees

It is recommended that data monitoring committees (DMCs), also known as data monitoring and safety committees (DMSCs) oversee all trials.[3] The purposes of DMCs are to:

- protect participant safety. The DMC may detect patterns of adverse events that may not be clear to investigators at individual sites because the DMC has access to data from all sites involved in a trial
- stop a trial as soon as a reliable conclusion is possible. Before a trial commences, interim analyses are planned to 'look' at the data to ensure a trial is not continuing after the result is clear. At this point, it may become unethical to randomise participants to a now known inferior treatment
- ensure continued scientific validity and necessity for the trial, ie. that no new evidence has accumulated since the trial commenced which may negate the genuine uncertainty that existed when the trial was conceived and make it redundant
- recommend stopping recruitment for the trial if it is unlikely to answer the original question (so-called futility). Several factors may persuade a DMC to finish a trial early due to futility:
  - slower than expected recruitment into a trial or fewer cases than expected may make the trial not viable to complete within a reasonable timeframe
  - outcomes in the treatment group are worse or equivalent to the comparison group, or
  - external factors such as running out of money to complete the trial
- enhance the trial credibility, as the DMC is a disinterested, unbiased body capable of making ethical, sound recommendations about a trial's future without the conflict of interest that investigators or trial sponsors may experience.[3]

Composition

Consideration of the membership and function of a DMC should be incorporated into trial planning at an early stage. However, as the DMC is an independent body, it will not be formally involved in the planning of the trial or with the ethics committee.

A DMC is composed of independent people with depth of expertise in clinical trials, the scientific basis of the treatment being tested, clinical management of the disease, biostatistics, ethics, and possibly consumer representatives. A more important consideration is who should not be on a DMC. The answer is anyone who has a vested interest in the trial outcome and/or is involved in any aspect of trial recruitment, measurement of outcomes, data handling or analysis. For the same reason, the deliberations of the DMC are kept confidential so as not to influence the conduct of those responsible for running the trial.

Associated costs

The issue of the costs associated with maintaining a DMC may be of concern to researchers, particularly in general practice research which is often performed with minimal resources. In our experience of local trials with minimal funding, membership of a DMC has been honorary and costs such as for travel are not reimbursed. However, in larger projects where substantial funding is available, reimbursement for DMC members' time and expenses should be budgeted for in the proposal and borne by the researchers. Paying a reasonable amount to compensate for the time involved is the norm is the USA, for

example. The cost of obtaining independent data analysis to provide a report to the DMC must also be included in budget calculations.

Tensions

The difficult task for DMCs is to balance the tension between the individual interests of patients about to be randomised in the trial and the collective ethics of obtaining quality evidence to guide appropriate treatment policies for the community who may gain future benefit from the results of the trial.[4–7]

Their deliberations will consider not only the interim analyses of the primary outcome and safety data, but also practical issues such as the rate of participant accrual and any new external evidence. Other considerations include the nature of the disease (if the condition being studied is rare, trials may be difficult to conduct, so a decision to terminate early may be taken more reluctantly) and what is already known about the treatment being tested such as background scientific evidence supportive of potential benefit or whether it has other proven benefits in the disease.[3,7–9]

The recommendations from the DMC after each interim analysis will be either to continue the trial, alter the protocol (eg. broaden the inclusion criteria if recruitment is too slow to be sustainable), suspend, or permanently cease the trial.

Interim analyses and stopping 'rules'

Data monitoring committees rely on reports from the researchers about adverse events and the results thus far in the trial. The researchers themselves remain 'blinded' to the trial results, so if the trial continues they will not be biased. Therefore, a data analyst not involved in the recruitment of participants or decision about terminating the trial is required to perform the interim analyses and provide a report to the DMC. The number and timing of interim analyses and the stopping rules set to make decisions about premature termination of the trial are planned before trial commencement.

Each 'look' at the trial data increases the risk of detecting a difference between the two therapies being tested by chance (type 1 error). For example, if there are five interim analyses all using the traditional level for a significant difference set at 5%, then the risk of finding at random a 'significant' difference at any of the analyses is 19%. There exists a tendency for 'regression to the truth' if the trial continues or as data accumulate from future trials.[5,8,10]

There are many statistical approaches available to guide DMCs in their recommendations regarding stopping a trial due to a positive result emerging. Stopping rules or guidelines set stringent criteria at each interim analysis to ensure the overall *p* value remains at or below 0.05 to reduce the risk of a type 1 error. Names of rules, which might be seen in papers reporting trial results, include: O'Brien and Fleming, Peto-Haybitte, Lan and DeMets. A practical approach is to use Bayesian methods to monitor trials where the strength of evidence is considered and expressed in terms of probabilities.[5,8]

The difficult responsibility for the DMC if interim results show a positive trend is the risk that, if the trial continues, new participants may receive inferior treatment. However, the decision to terminate a trial early based on favourable interim results, among other considerations as above, may have negative impacts. It may reduce the credibility of the trial, the results will be less precise (have wider confidence intervals), the interpretations may be prone to bias and, although reported in the medical press with appropriate caveats such as early stopping or small numbers, may be interpreted differently once released to the public.[7]

Somewhat neglected in textbooks and papers about stopping rules is the opposite situation that DMCs also may deal with: at interim analysis, there is either an emerging negative trend or no difference between the study groups. The approaches to deal with these outcomes are different to a positive trend and less well defined, as ethically, DMCs require weaker evidence to terminate a trial early in these circumstances.[5,8,11] The risk in this circumstance for the DMC is that premature termination on insufficiently convincing evidence may inhibit medical science from answering an important therapeutic question – is this treatment beneficial, neutral or actually harmful? In making their decision, DMCs may consider:

- the minimum difference between the treatments being tested that would change clinical practice
- whether the trial is likely to ever be repeated. If not, it may be ethical to continue the trial to gain as much information as possible if safety is not a concern
- recommending that the trial be stopped early if the chances are small of reaching a statistical significant result by the end of the trial, and
- whether the treatment being tested already has other positive trial evidence or is in widespread use. If so, the DMC may require a more extreme negative trend before early termination than with a new treatment with little or no other evidence.

Researchers generally embark upon a trial with optimism of a positive outcome and in these circumstances it is understandable that planning for futility may be neglected. However, guidelines for stopping the trial early due to positive, null and negative effects should be set *a priori*, both to guide the DMC and ensure decisions are made rationally before other events such as long hard recruitment periods or other trial disasters intervene.

Conclusion

Randomised controlled trials are expensive and resource intensive, yet essential to build a sound evidence base for health care professionals and consumers to make treatment decisions. Randomised controlled trials are based on ethical principles which aim to balance the needs and safety of individuals being randomised to a trial treatment group and those of the community who will benefit from the results of the trial.

A DMC is an independent body that oversees the conduct of a trial. Based on the results of interim analyses of trial data and other considerations such as adverse events

and previous knowledge about the treatment; the DMC makes recommendations to the researchers about the continuation of the trial. Statistical methods are applied to interim results in an attempt to ensure that false positive statistically significant results do not unduly influence the decision of whether to continue the trial. While balancing the ethical requirements of the trial, the question for the DMC is how much evidence is needed to convince regulators, scientists, doctors and patients that a treatment is effective or not effective.

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