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Chapter 7 Trial governance

1. Introduction to trial governance

Since the first edition of this book was published in 1991, there has been a very large increase in the number of **field trials of health interventions** being conducted in LMICs and, in parallel with this expansion, an increasing number of regulations and guidelines put in place to govern the conduct of clinical trials. Most of these regulations have been developed in the context of clinical trials in HICs, particularly with respect to the evaluation of new drugs and vaccines, but there is a strong expectation, and in many instances a requirement, that these regulations are followed, no matter where a trial is conducted.

A particularly important development occurred in 1990 when representatives of regulatory authorities and pharmaceutical companies in Europe, Japan, and USA agreed on scientific and technical aspects of drug registration. Guidelines were developed from their deliberations called ‘The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use’, commonly known by the initials ‘ICH’. Since then, ICH has evolved, in response to the increasingly global nature of pharmaceutical development, with the mission to achieve greater harmonization in the planning, conduct, and reporting of trials to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner (<<http://www.ich.org>>).

In this chapter, we highlight aspects of trial design and conduct that have evolved significantly in recent years, particularly with respect to the role of the sponsor, the functioning of steering committees and data safety and monitoring boards (DSMBs) and requirements for trial registration.

2. The trial sponsor

Whenever a field or clinical trial is conducted that involves human participants, it is necessary that an individual, or more commonly an institution, has legal responsibility for the trial, ensures that the trial is conducted properly, according to a defined protocol, and has overall responsibility for the management and financing of the study. This person, or institution, is known as the *sponsor* of the trial. While, in principle, the PI of a trial may act as the sponsor, for legal reasons most institutions prohibit members of their staff from taking on this role and insist that there is institutional sponsorship. In the case of the trial of a new pharmaceutical product, the sponsor is usually the company that is developing the product. With respect to trials of licensed products or trials that do not involve specific products (for example, hygiene interventions), the sponsor would generally be the agency that is funding the trial or the research institution or university of those conducting the trial. Many funding agencies are not prepared to act as the sponsor for the studies they fund, unless those conducting the study are directly employed by the agency, and, in such cases, the institution employing the PI will generally take on the role of sponsor. In such situations, the sponsor is not responsible for financing the trial directly but does have responsibility for arranging that the funds needed to conduct the trial to a high standard are available from the funding agency and for administering the grant. The sponsor also has legal liability for any harm that might arise during the conduct of the trial.

The sponsor must ensure that the trial meets all relevant standards and regulations and must ensure that arrangements are put in place for carrying out the trial, for monitoring that it is being conducted properly, for meeting all required ethical standards (see Chapter 6), and for reporting the results of the trial at the end of the study. The sponsor also has responsibility for ensuring the safety and well-being of participants in the trial and for ensuring that treatment and care are available, usually free of charge, for any trial participants who are harmed as a consequence of their involvement in the trial.

Usually, sponsors will delegate different elements of their responsibility to the trial’s PI, steering committee, or DSMB, but the sponsor remains ultimately accountable for all aspects of the governance of the trial, whether or not some components have been delegated.

For clinical trials of drugs and vaccines and, in some cases, also for other interventions, national regulatory authorities usually require that the sponsor has insurance or indemnity for any potential liabilities of the sponsoring institution

and the investigators in the trial. Whether or not this is required, it is a good idea, as the cost of any legal action taken against the trial could be considerable. The regulations will also often require that the sponsor ensures that the trial conforms to GCP (see Chapter 16), for which guidelines have been also produced by ICH (International Conference on Harmonisation, 1996).

The PI of a trial is accountable directly to the sponsor. Furthermore, although any reports from a steering committee or DSMB are formally to the sponsor, the sponsor may delegate responsibility for receiving and acting upon such reports to the PI. Similarly, the sponsor has the formal responsibility for liaison with those who have an oversight responsibility for the trial, such as the funding agency and relevant ethics committees. Formally, therefore all communication between these bodies and, for example, the trial steering committee or the DSMB, and vice versa, should be through the sponsor.

3. Steering committee

It is common in large trials, particularly multicentre trials, for a steering committee to be set up, to which the PI reports and from which the PI may seek guidance or authorization, with respect to aspects of the conduct of the trial. These will include any significant protocol amendments, which will also usually have to be approved by the ethics committees which approved the original protocol for the trial. There is no obligation on an investigator to set up such a committee (unless required by the funding agency), and, for smaller trials, a steering committee may be considered unnecessary. Such a committee should usually consist of senior investigators in the trial, together with appropriate independent experts.

The role of a trial steering committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The trial steering committee should agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. The steering committee often has responsibility for approving the analytic plan for a trial (see Chapter 21, Section 3)—see also the ICH guidelines on statistical principles for clinical trials (International Conference on Harmonisation, 1998). The committee will usually have some members who are independent of the investigators, and, in particular, the chairperson should be independent. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the trial steering committee, advised by the DSMB (see Section 4).

The trial steering committee is distinct from a trial management group, which normally includes those individuals responsible for the day-to-day management of the trial such as the PI, statistician, trial manager, and data manager. The role of the management group is to monitor all aspects of the day-to-day conduct and progress of the trial to ensure that the protocol is adhered to and to take appropriate action to safeguard participants.

4. Data and Safety Monitoring Board

For trials of interventions that may entail the possibility of significant harm, as well as benefit, to participants, the trial sponsor should establish a DSMB—sometimes termed a committee (DSMC), a Data Monitoring Board (DMB) (or Committee (DMC)), or Independent Data Monitoring Committee (IDMC). The DSMB is independent of those conducting the trial and separate from the ethics review committee (ERC) to monitor the safety of the trial, while it is being conducted. Not all trials will require a DSMB, but listed in Box 7.1 are the types of trial for which WHO has recommended that it would be considered desirable to set up such a committee (World Health Organization, 2005).

A DSMB will usually be set up for trials which are double-blind, in which the investigators and sponsor do not know which intervention individual participants have received, but the DSMB will have access to the randomization code, which it can break during the course of the trial for specific reasons, including safety concerns or interim analyses (see Section 4.1.3). For trials where the intervention allocation is not blinded, the investigators and the sponsor can assess on a continuous basis if there is an excess of AEs in one of the intervention arms of a trial. Even so, it is usually a good idea to have a DSMB, as this committee may take the responsibility for advising the PI, steering committee, and sponsor on critical decisions, such as whether to stop a trial because of adverse effects or signs of failure of the intervention during the course of a trial. Although members of DSMBs are often not paid for their services, a budget will still be required to cover their meetings and any visits they may need to make to the trial site(s).

In this section, we outline the functions and responsibilities of a DSMB, the selection of members, the major issues with which it has to deal, and lines of reporting to those involved in the trial.

4.1. The functions of a Data and Safety Monitoring Board

The prime function of the DSMB of a trial is to safeguard the welfare of participants in the trial. A key aspect of this is to monitor the occurrence of adverse events (AEs) by trial arm and to recommend action to the investigators in the event of finding evidence of harm. In ‘blinded’ trials, the DSMB will be the only group to have access to the randomization codes during the conduct of the trial, so that, if necessary, they can ascertain which intervention an individual participant received. The DSMB may also be called upon to ‘break the code’ for a trial at pre-specified time points to make a recommendation as to whether or not a trial should be stopped prematurely because of ‘overwhelming efficacy’ or ‘futility’.

4.1.1. Monitoring the conduct of the trial

An important aspect of safeguarding the welfare of trial participants is to check that trial procedures are being followed, according to the protocol, and there are no significant deviations from the trial plan. If there is a trial steering committee, responsibility for monitoring trial conduct will lie principally with that committee, and the DSMB should receive reports from the steering committee—often the chair of the DSMB attends all or part of the steering committee’s meetings. However, if there is no steering committee, then the responsibility for monitoring trial conduct falls more heavily on the DSMB. Usually, this function is satisfied by the DSMB receiving detailed reports from the investigators on the progress and conduct of the trial at each DSMB meeting, but DSMB members may also make visits to the trial sites. Day-to-day monitoring of trial procedures, including data collection, is often provided by clinical trial monitors (see Chapter 16, Section 7.2) who should report regularly to the sponsor. If there are issues of concern, the sponsor has responsibility for reporting these to the DSMB, through the steering committee if there is one. Clearly, monitoring the conduct of a trial can be a major undertaking, and exactly what part the DSMB is expected to play in this should be detailed in the DSMB Charter (see Section 4.3).

4.1.2. Monitoring the safety of trial participants

Different kinds of AE should be reported to the DSMB on an ‘immediate’ or regular basis, the frequency depending on the seriousness of the AE .

Any serious AEs (SAEs) (see Chapter 12) that are judged by the investigators to be likely to have been due to the intervention (‘potentially intervention-related SAEs’) should be reported very quickly to the DSMB, within a few days of their occurrence or their first notification to the trial investigators. Similarly, any deaths among trial participants, whether or not judged related to the intervention, should be immediately reported to the DSMB. As much relevant detail as possible should be provided to the DSMB about the nature and circumstances of the death or SAE, along with a cumulative update of all such events. Deaths and potentially intervention-related SAEs would normally be reported to the sponsor at the same time as being reported to the DSMB. When such events are reported, the chair of the DSMB should communicate with members to ascertain if any members consider the events are sufficiently serious and linked to the intervention that they require further investigation or, in extreme cases, might require that the trial is paused or terminated. If major changes to the conduct of the trial are suggested, the committee would generally meet by telephone conference or have a face-to-face meeting.

For SAEs that are not considered by the investigators to be directly related to the intervention, the DSMB should be informed of these on a regular basis, possibly monthly, depending on the size of the trial. At regular meetings of the DSMB, the accumulated SAEs should be considered. They should be classified by the type of SAE (for example, by hospital admission diagnosis), when they occurred in relation to the application of the intervention, and whether they affected participants in the intervention or control group. Displaying data by intervention and control groups requires breaking the code, and this is usually done either by an independent statistician (i.e. not one of the investigators, but a statistician contracted by the sponsor to perform the analyses) or by a statistician on the DSMB. Ideally, the tabulations should be presented to the DSMB by trial arm, without specifying what each arm has received intervention or control, and they should consider whether they are concerned by the size of any relative excess of events in any of the trial arms. Only if the answer to this question is ‘yes’ should they ask which arm was which. This procedure is adopted to avoid unnecessarily exposing the DSMB to unblinded data, unless there is good reason for concern, and to avoid their being biased in their assessment of the distribution of SAEs by knowing which arm any excess is in.

For more minor AEs, such as a minor local reaction to a vaccine or mild nausea, the DSMB can be presented with analyses of these on an occasional basis, though usually this should happen at least once a year. Again, they should

initially be presented without identification of what each arm has received. Data on AEs are usually presented for information, rather than action, though occasionally action might be considered if there is a substantial excess of AEs in the intervention arm.

4.1.3. Conducting interim analyses

In some trials, a plan is made to examine interim efficacy results before the trial's expected end date. There are two main reasons for doing this. First, if the intervention proved much more effective than anticipated, then there might be grounds for terminating the trial early on the basis of 'overwhelming efficacy', such that it might not be considered ethical or necessary to continue with a control arm. Such analyses and their timing should be clearly specified in the trial protocol, as should the circumstances in which the results would lead to a recommendation to terminate the trial. In other words, the 'stopping rule' should be predefined. Second, the DSMB might recommend stopping a trial because of 'futility' if the interim results show a difference in study outcomes between the intervention group and the control group which is much less than expected if the intervention is effective and it is clear that, even if the trial is continued until its planned end, it is very unlikely to show an important difference in the rates of the primary outcome between the two groups. Again, such analyses should be planned in advance of starting the trial, and the stopping rules specified in the trial protocol. The DSMB has responsibility for conducting these analyses, because they require breaking the code of the trial; if the decision is to continue the trial, the investigators have not been compromised by knowing either the interim results or which participants were allocated to which intervention. In such circumstances, the DSMB should not be tempted to share the interim results with the investigators but should merely tell them to carry on as planned. Having an independent DSMB is very valuable if a decision needs to be made about stopping a trial early, because this usually has considerable logistic and funding implications and may not be popular with the investigators, staff (who may even need to be laid off early), or participants.

Another common reason for conducting an 'interim' analysis is if the incidence of the primary outcome in the trial is less than anticipated or if recruitment to the trial is slower than expected. In such circumstances, it may be clear that the funds for conducting the trial will be exhausted before the planned number of participants or outcome events has been achieved. The investigators may then wish to seek further support from the funding agency to complete the trial. That agency may well request an interim analysis to know if the results to date already show the one arm of the trial to be convincingly superior to the other(s) or, conversely, whether there is little difference between the results in the different arms of the trial and collecting further data is unlikely to produce a convincing result, so it would be futile to extend the trial.

4.1.4. Modification of trial procedures and other advice

During the course of a trial, there may be a need for the DSMB to recommend modifications to the study, because of considerations of patient safety such as eligibility criteria, dosages, treatment duration, and/or concomitant therapy. When there is a trial steering committee, the DSMB would normally propose these recommendations to that committee (as representing the sponsor).

In the absence of a trial steering committee, investigators may well turn to the DSMB for advice on other aspects of the conduct of the trial. The DSMB is a useful source of independent unbiased advice, especially as it will often include persons with substantial trial experience.

4.1.5. Reporting to the sponsor

After each meeting of the DSMB, minutes should be drawn up relating to confidential and non-confidential parts of the meeting. In the non-confidential parts of a meeting, the trial investigators or their representatives may be present, in order to update and inform the committee on the progress of the trial, any deviations from planned procedures, and any AEs among trial participants. Confidential (closed) parts of the meeting will be restricted to DSMB members and may involve looking at data from the trial on outcome measures or AEs, unblinded with respect to the intervention arms. The minutes of this part of the meeting should be kept securely and confidential to the DSMB members until the end of the trial, at which time they should be given to the sponsor.

At the end of each of its meetings, the DSMB should draw up a report to the sponsor. This is often short and along the lines of 'We have reviewed the safety and other data from the trial and find no evidence of a safety concern that would lead us to suggest any change to trial procedures at this time'. However, if discussion of the trial data does cause the DSMB specific concerns and leads them to suggest specific changes to the conduct of the trial, these should be

conveyed to the sponsor. The most extreme advice would be to halt the trial, but other advice might suggest, for example, changes to trial procedures, such as more frequent reporting of SAEs to the DSMB, more careful follow-up of a subset of participants, or changing diagnostic methods.

Sometimes, the investigators or sponsor will seek specific advice from the DSMB on aspects of trial procedures. For example, in some trials, the DSMB, or a subset of its members, may be asked to classify suspected cases of the disease of interest, according to levels of diagnostic certainty (without knowledge of which intervention they received)—though, depending on its composition in terms of expertise, this role might also be assumed by the steering committee or contracted to other independent experts (sometimes referred to as an ‘endpoint committee’).

It is important to note that the normal line of responsibility for reporting the deliberations of the DSMB is from the chair of the DSMB to the sponsor, and the responsibility for liaising with investigators and ethics committees lies with the sponsor. Sometimes, the sponsor will delegate this role to the trial steering committee, so that the DSMB reports directly to that committee. However, the DSMB should not report directly to the trial investigators, unless delegated to so do by the sponsor.

4.2. Composition and appointment of the Data and Safety Monitoring Board

The membership of a DSMB is usually decided by the trial sponsor, or the sponsor may delegate this task to the PIs or to the trial steering committee. Persons invited to join a DSMB are typically independent experts in the area of study of the trial, either working in the same field or in a related discipline, who have no personal or professional involvement with the intervention being tested, in that they will not profit either professionally or financially, according to the outcome of the trial. That is, the membership should be persons who are considered to be unbiased experts. Persons with strong views about the relative merits of the interventions under test would generally be considered unsuitable for DSMB membership. Those invited to join the committee should usually be familiar with, or have experience of, the conduct of RCTs. The chair of the committee should certainly have such experience and ideally should have experience of previous service on a DSMB.

The size of a DSMB will vary, according to the size and complexity of a trial and the likelihood that any of the trial interventions or procedures may cause significant harm to participants. The minimum size is three, and it is rare to have more than ten members, though the DSMB of large multicentre trials may approach that upper limit. The typical composition of a DSMB is outlined in Box 7.2.

In multicountry trials, it is common to have DSMB members drawn from at least some, if not all, of the countries included in the trial. Whether or not (lay) community members or advocates are included as members varies between trials. The inclusion of such members may help bring to the DSMB the perspectives of the population under study. Such members should not be participants in the trial, but the member could be someone with the disease or condition under study or a close relative of such an individual. For example, it has been common to include such persons in trials of HIV vaccines, but practice varies in trials of other interventions, and often lay members are not included.

For ‘high-profile’ trials of interventions, or with study procedures that might be controversial or have unusually high risks, the DSMB might include a medical ethicist knowledgeable in the design, conduct, and interpretation of clinical trials.

Anyone appointed to a DSMB must be prepared to respect the strict confidentiality of the discussions that take place within the committee and of the data that the committee may be given access to. They may also require training, for example, in the principles of GCP. Such training is now widely available either online (which is often free) or face to face.

Generally, members of a DSMB are not paid, but they may be recompensed for loss of earnings, travel, and other expenses incurred as a consequence of DSMB membership. However, in some industry-sponsored trials, members may be paid a fee for their participation.

Before an individual is appointed to a DSMB, it is important that they are given the opportunity to study the trial protocol, so that they fully understand the purposes of the trial and how it will be conducted. Often they will also be given the opportunity to suggest changes to the protocol—especially related to issues such as reporting of AEs and trial stopping rules. Once more, it is important to stress that their advice should go to the sponsor and the trial steering committee, and not directly to the investigators.

4.3. The Data and Safety Monitoring Board charter

In many trials, a specific ‘charter’ is drawn up by the sponsor that details exactly the terms of reference and responsibilities of DSMB members. The charter should take account of the particular needs of the trial and the questions it is addressing. It should detail the relationship between the DSMB and the sponsor, investigators, steering committee, ethics committees, and others with responsibilities in the study. It also gives details of how meetings will be organized, how often they will take place, how many members constitute a quorum, and how confidential and non-confidential minutes will be produced, distributed, and stored securely until the end of the trial. All members of the DSMB will be required to sign the charter at the time of their appointment. Guidelines are available on drawing up a DSMB charter (DAMOCLES Study Group, 2005).

5. Trial registration

Until relatively recently, there were no comprehensive sources of information about ongoing clinical trials. Not infrequently, trials would be started and would be prematurely ended with knowledge of their conduct known only to those closely associated with the trial if the findings were not published in the medical literature. Other trials were completed, but their results were never reported for various reasons, including that the investigators or sponsors did not like the findings of the trial! Other investigators might start a new trial, ignorant of the fact that a trial addressing essentially the same question was already under way or had even been completed but not yet published. Those conducting systematic reviews (see Chapter 3, Section 2) would be aware of the published literature but would be ignorant of such unpublished trials. It has been well documented that trials that show a ‘positive’ outcome are more likely to be published than those that do not, and thus the published literature may constitute a biased sample of all of the evidence related to the effects of a specific intervention.

In the 1990s, it was proposed that registers should be set up, in which those conducting trials should be required to record their trial before the first participant was enrolled into it. The record should consist of basic information about the trial (Box 7.3). This recommendation was given teeth in 2005 when the International Committee of Medical Journal Editors (ICMJE), which comprises the editors of many of the major journals that publish papers on the results of trials, made it a requirement for publishing that the trial should have been properly reported to a public clinical trials register before any participant was enrolled into the trial (<<http://www.icmje.org>>). Initially, the requirement covered only randomized clinical trials, but it has been subsequently expanded to include ‘any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes’, so that Phases I and II trials and non-randomized intervention studies, as well as Phase III RCTs, are included.

Several coordinated trial registries have been set up, so that any individual trial is issued a unique number which is recorded in the International Standard Randomised Controlled Trial Number Register (<<http://www.controlled-trials.com/isrctn>>). Trials are only eligible for publication by ICMJE journals if they have been registered in one of the following registries:

- ◆ <<http://www.anzctr.org.au>>
- ◆ <<http://clinicaltrials.gov>>
- ◆ <<http://www.isrctn.org>>
- ◆ <<http://www.umin.ac.jp/ctr/index.htm>>
- ◆ <<http://www.trialregister.nl/trialreg/index.asp>>
- ◆ <<http://eudract.ema.europa.eu>> (new registrations after 20 June 2011), or
- ◆ any of the primary registries that participate in the WHO International Clinical Trials Portal (see <<http://www.who.int/ictrp/network/primary/en/index.html>>). This includes the Pan African Clinical Trials Registry (<<http://www.pactr.org>>). This registry enables African trial registration for those who do not have reliable access to the Internet.

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Boxes

Box 7.1 WHO recommendations for the types of trial for which a DSMB is relevant

- ◆ Controlled studies with mortality and/or severe morbidity as a primary or secondary endpoint.
- ◆ Randomized controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality.
- ◆ Early studies of a high-risk intervention (risk of non-preventable, potentially life-threatening, complications; or risk of common, preventable AEs of interest (especially adverse drug reactions)), whether or not randomized.
- ◆ Studies in the early phases of a novel intervention, with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes.
- ◆ Studies where the design or expected data accrual are complex or where there may be ongoing questions with regard to the impact of accrued data on the study design and participants' safety, particularly in studies of a long duration.
- ◆ Studies where the data justify an early termination such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality.
- ◆ Studies carried out in emergency situations.
- ◆ Studies which involve vulnerable populations.

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Box 7.2 Typical composition of a DSMB

- ◆ At least one clinician with knowledge of the disease(s) under study.
- ◆ A biostatistician knowledgeable about statistical methods for clinical trials and, if interim analyses are to be conducted, knowledgeable about the specific issues related to sequential analysis of trial data.
- ◆ At least one clinician or scientist familiar with the kinds of intervention(s) under test and their possible adverse effects.
- ◆ Others who bring special expertise to the committee relevant to the intervention or its application such as toxicologists, epidemiologists, and clinical pharmacologists.

It is possible for a single individual to cover more than one of these skill areas.

Box 7.3 (Minimal) information that is required when registering a clinical trial

- ◆ Title of the trial.
- ◆ Acronym for the trial (if there is one).
- ◆ Study hypothesis/trial objective, i.e. what question(s) is the trial design to address.

- ◆ Ethics committee approval—which committees and when approved
- ◆ Study design—individual or cluster, whether or not randomized, double-blind, etc.
- ◆ Countries of recruitment.
- ◆ Disease/condition/study domain—nature of study population and diseases of interest.
- ◆ Inclusion criteria for participation in trial.
- ◆ Exclusion criteria for participation in trial.
- ◆ Anticipated trial start date.
- ◆ Anticipated trial end date.
- ◆ Current status of trial—ongoing, waiting ethics approval, etc.
- ◆ Patient information material—is information about the trial publicly available and where?
- ◆ Target number of participants.
- ◆ Description of the interventions (for example, name, dose, duration).
- ◆ Primary outcome measures.
- ◆ Secondary outcome measures.
- ◆ Sources of funding.
- ◆ Trial website (if there is one).
- ◆ Publications.
- ◆ Name and contact details for PI and, where different, of person(s) responsible for providing information about the trial to the public and the scientific community.
- ◆ Name and contact details for sponsor.

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