4.10: Analysis, monitoring, and reporting

10.1 Planning the main analyses

The main analyses that are expected to result from the trial should be developed in some detail, with the use of dummy tables. Such an exercise is a great help when planning the trial, as it helps clarify exactly what data are actually needed and highlights redundant data. All specific objectives should be tied to planned analyses.

10.2 Analyses during the trial

Analysing relevant data from a trial, as they accumulate during the trial, is an important way of monitoring the satisfactory progress of a trial. Administrative analyses of the numbers of participants recruited each day or week and of the data collected by different fieldworkers are important for QC. A running tally should be kept of the numbers of participants experiencing the various trial endpoints to verify that the estimates of incidence rates used to plan the size of the trial were appropriate. Ideally, the investigators will be blind with respect to which interventions have been allocated to which participants, but differences between the different interventions might be analysed by a data and safety monitoring committee (as discussed in Section 10.3). Other aspects of interim analyses are discussed in Chapter 5, Section 7.1 and Chapter 7, Section 4.1.3.

Increased reliance on the use of smart phones or personal data assistants (PDAs) to record data when interviewing participants facilitates real-time data quality checks and analyses. Considerable ahead-of-time preparation and planning, however, are necessary, in order to programme devices to be able to produce such analyses regularly.

Interim reports, based on such ongoing analyses, may be required during the course of a trial by national authorities and by the trial’s funding agency, in order to check that the original proposal is being adhered to and that the assumptions
underlying the trial design were correct.

10.3 Data and Safety Monitoring Committee

For large trials, it is advisable for the investigators to set up an independent DSMC. Such a committee generally has access to selected unblinded data during the course of a trial and, for example, will conduct analyses to monitor whether there are an unacceptable number of adverse events (AEs) associated with an intervention. In such circumstances, the committee may recommend changes to the design of the trial or, in more extreme cases, that the trial be stopped, either temporarily or permanently.

The DSMC might also be charged with conducting interim analyses of the trial with respect to the primary endpoint, so that if the efficacy of intervention is substantially lower or substantially higher than expected, changes to the trial design, including early stopping, might be recommended.

The roles and functioning of DSMCs are discussed in Chapter 7.

The most important function is usually to hold the randomization code for the trial and to monitor the results of the trial, both in terms of effectiveness and safety, as they accumulate. If there is evidence of a substantially increased risk of adverse reactions associated with any of the interventions under study, the committee would have the power to advise the Trial Steering Committee to stop further recruitment. Similarly, if evidence accumulates that one intervention is substantially better than the others (or one is substantially worse), the committee would usually recommend that the trial be ended or that at least one of the trial arms is discontinued. In blinded trials, a major advantage of these functions being undertaken by an independent committee is that the investigators can remain blind to the randomization codes, which is an important way of ensuring unbiased assessment of the trial endpoints. But, even where the trial is not blinded, it still has the considerable advantage of ensuring that the recommendation of stopping or continuing a trial is as objective as possible, because stopping a trial early usually has considerable logistic implications and may not be popular with the investigators, staff (who may even need to be laid off early), or participants.

The circumstances in which a trial will be prematurely ended should be carefully considered when the trial is being designed, and the DSMC should be party to such discussions. It will not be possible to predict all possible situations that may cause a decision to be taken to end a trial, but this should be done to the extent possible. In particular, there should be consideration as to how large a difference may be apparent between the interventions, with respect to their impact on specific endpoints, before it is decided to end the trial. In some circumstances, it may be important to go on beyond the point where statistical significance is reached. These issues are discussed in Chapter 5, and there are also ethical considerations which are discussed in Chapter 6. The DSMC might also set up independent QC checks on trial procedures and, for example, may arrange to review the diagnoses of all cases of the diseases of interest arising in the trial (which should be done, of course, ‘blind’ to knowledge of the randomization codes).

The committee usually works on a pro bono basis and does not have auxiliary staff. If its activities will require QC checks or diagnostic reviews, it may be necessary to budget for these activities when preparing the protocol.

In some trials, the DSMC may consist of one person, sometimes called the ‘clinical monitor’.
10.4 Analysis methods

The analysis of a large field trial will usually be a complex undertaking and will usually require the involvement of a professional statistician, sometimes under supervision of a senior statistician or epidemiologist. It is not feasible in a manual of this kind to detail all of the analysis methods that it might be appropriate to employ in different trials. However, in Chapter 21 an outline is given of the main methods of analysis that are likely to be employed. It is included as it summarizes relevant methods that are not covered as comprehensively in the most basic epidemiological texts or books on medical statistics.

10.5 Reporting results

Once a field trial has been completed and the results analysed, it is essential that the results and their implications are made available to the scientific community, to those who participated in the trial, and to those responsible for designing and implementing regional and national disease control strategies. These aspects are discussed in Chapter 23.

10.6 Further studies

Many trials will provoke questions amenable to further research. One example might be if a trial of a hookworm vaccine shows that it provokes good specific antibody- and cell-mediated immune responses and reduces the incidence of infection by 80% but is associated with prohibitive adverse reactions, further studies may well be needed to explore which antigens are causing the adverse reactions and whether removing these will also reduce the vaccine’s effectiveness against hookworm.

Alternatively, if a trial of traffic-calming measures in one city shows that they are highly effective in reducing road traffic accidents, questions may well arise on how best to implement similar measures in other settings and/or to monitor the effectiveness of such interventions when implemented on a wide scale and over a long period of time. Such studies are often called Phase IV studies, as they evaluate interventions in real-world settings after the Phase III trial has been completed. These are discussed in Chapter 22.