5.7: Other factors influencing choice of trial size

7.1 Allowance for interim analyses

It is sometimes desirable to incorporate interim analyses into the trial plan, involving review of the results at (say) 6-monthly or annual intervals. If an interim analysis indicates that there is already strong evidence of the superiority of one of the interventions under study, the trial can be terminated in order that participants are no longer subjected to an intervention which is known to be inferior. The incorporation of interim analyses may be particularly valuable if the trial is planned to continue for several years, with the gradual accumulation of cases of the outcome of interest, or if individuals or communities are entered into the trial sequentially.

There are also disadvantages in carrying out interim analyses, however. If the trial is terminated early, because the intervention appears to be beneficial, there may be no opportunity of detecting any long-term effects of the intervention, including how efficacy changes with time or long-term adverse consequences of the intervention. Also, although a significant effect of the intervention may be demonstrated, the precision of the estimate of effect may be too low to be of much value.

If, after careful consideration, it is decided that interim analyses are to be conducted, these need to be planned in the trial design. It is necessary to employ a more stringent significance level for each analysis (interim and final) to maintain the same overall level of significance.

Details of the implications of interim analyses are given by Geller and Pocock (1987). As a rough guide, the following approach is suggested. It is rarely advantageous to plan for more than three or four interim analyses. It is recommended therefore that, for trials planned to continue for 2–4 years, the trial plan should include no more than two interim analyses (plus the final analysis). To compensate for this, the maximum trial size (i.e. the maximum person-years of
observation if the trial proceeds to completion) should be increased by about 15%. A stringent significance level of \( p = 0.01 \) should be used at each interim analysis to decide whether or not the trial should be terminated. This means that, if the trial proceeds to completion, an unadjusted \( p < 0.04 \) would correspond to an adjusted \( p < 0.05 \) if the interim analyses are taken into account, i.e., little power has been lost in performing the interim analyses.

### 7.2 Allowance for losses

Losses to follow-up occur in most longitudinal studies. Individuals may be lost, because they move away from the trial area, they die from some cause unrelated to the outcome of interest, they refuse to continue with the trial, they are away from home at the time of a follow-up survey, or for some other reason.

Losses like these are of concern for two reasons. First, they are a possible source of bias, as the individuals who are lost often differ in important respects from those who remain in the trial. Second, they reduce the size of the sample available for analysis, and this decreases the power or precision of the trial.

For these reasons, it is important to make every attempt to reduce the number of losses to a minimum. However, it is rarely possible to avoid losses completely. The extent of the problem will vary, according to circumstances, but, as a rough guide, in a longitudinal trial of a rural community with 2 years of follow-up, losses of around 20% would not be unusual.

The reduced power or precision resulting from losses may be avoided by increasing the initial sample size, in order to compensate for the expected number of losses. For example, if sample size calculations suggest that 240 subjects are required and a 20% loss rate is expected, the sample size should be increased to 300 (because 80% of 300 gives 240). It is important to stress that sample size inflation only deals with the problem due to the reduction in the size of the sample available for analysis; it does not solve any potential problems due to bias. So, even if the sample size has been inflated to allow for losses to follow-up, it is still necessary to strive to minimize losses, in order to avoid bias.