12.3: Factors influencing choice of outcome measures

The choice of the outcome measures in a specific trial largely depends on the purpose of the trial and how relevant, feasible, and acceptable the measures will be in a particular study population. Furthermore, the choice may be constrained by economic, logistic, or ethical considerations.

3.1 Relevance

Interventions are generally designed to reduce disease and/or to promote health. The outcome measures chosen should reflect these objectives as fully as possible, but, when intermediate variables are used, rather than those of main interest, care must be taken to choose variables of direct relevance to the main outcome. This is not always straightforward. For example, it may be decided to assess the impact of a vaccine by measuring the proportion of individuals who develop antibodies to the vaccine. This may be reasonable if it is known that there is a high correlation between the development of antibodies and protection from clinical disease. For many diseases, however, this relationship has not been established, and it would not be warranted to base conclusions regarding protection against disease simply on antibody determinations.

A health education intervention may be designed to change behaviour to reduce disease risk, but, as discussed in Section 2.5.1, asking individuals if they have changed their behaviour may give a measure of impact that correlates poorly with true changes in the risk of disease. Are individuals responding truthfully? Are they doing what they say they do? Even if behaviour changes, is this associated with a lowering in the incidence of disease?

The outcome variable measured should be as close as possible to the outcome of main interest. While this may seem an obvious suggestion, it may have major impact on the design of a study. For example, if the prevention of death is of prime interest, then, whenever possible, this should be made the endpoint of the trial. To do so might require an increase in the size of the trial from hundreds to thousands, or even tens of thousands, of individuals. Such a large trial
might be difficult to find funding for, and there may never be an adequate test of whether the intermediate variables measured are acceptable surrogates for effects on mortality.

3.2 Feasibility

To be successful, a trial must be designed to have achievable objectives. A trial which has mortality as the endpoint, but which is too large to be successfully completed, may be of less value than a well-designed smaller trial aimed at assessing the impact on some intermediate endpoint such as severe disease. There must often be a compromise between relevance and feasibility. It is pointless to set unachievable goals, even if they look attractive in the objectives section of a proposal. Also, it may be of little value to measure the effect of an intervention on an outcome measure which is only distantly related to the measure of prime interest. The outcome measures selected will be much influenced by the resources available for the trial, the availability of skilled personnel, and the necessary laboratory support to diagnose cases of disease. In many large trials, every individual in the study population may have to be screened for disease or infection in a relatively short time. With such time constraints, some individuals may be misdiagnosed. The consequences of reductions in diagnostic sensitivity and specificity are discussed in Section 4.2.

3.3 Acceptability

The acceptability of the measurement of an outcome variable to the study population is critical to the successful conduct of a trial. For example, the recording of birthweights may not be possible in a population that allows only close relatives to have access to a mother for a few days or weeks after the child’s birth. Taking venous blood samples or repeated blood samples is unpopular in many societies. If the method for measuring the outcome involves pain or inconvenience to the participants, it may be necessary to modify or abandon it. An outcome, of which the assessment involves a long interview with participants at a time when they would otherwise be planting crops or taking care of their household chores, may be unacceptable; it may either have to be abbreviated or carried out at a more convenient time.

3.4 Opportunity for add-on studies

Some trials offer the opportunity to measure outcomes that are not directly related to the objectives of the original study itself. These opportunities can be exploited by researchers to answer questions with minimal additional funding. For example, a diarrhoeal surveillance study might be carried out within a clinical trial in which a cohort of healthy children is being followed over time. However, it is very important that the add-on study does not interfere with the original study outcome measure. Such additions should be considered at the beginning of the study and should have a separate study protocol. It is also important to inform sponsors, participants, and all stakeholders of the original trial of the coexistence of the proposed add-on study. Such investigations will usually require separate ethical approval and informed consent.