12. STOPPING RULES FOR TRIALS

The duration of treatment for the individual patient is specified at the design stage as is the total number of subjects to enter the trial. In the normal course of events the trial will last as long as it takes to enter the required number of patients and for the last patient to complete the study. However, the trial may be abandoned early if adverse effects of treatment are observed, if a benefit is demonstrated at the predetermined level of significance, or if it is apparent that the required number of patients will never be recruited or that the response to treatment is not as expected.

From the ethical point of view it is important to minimise the number of subjects receiving the inferior treatment. This will be achieved by stopping the trial when an 'almost certain' advantage has been detected for one of the randomised groups. The ethical aspects are discussed in chapter 3, pages 41-43.

Decision rules for stopping the trial must be agreed at the design stage and in a long-term trial a data monitoring committee or Data and Safety Monitoring Board (DSMB), must examine the results of the trial at given points in time. The decision to stop must be made by an independent committee, such as the Advisory Board discussed in chapter 8.

The decision rules for stopping the trial will be discussed together with the disadvantages of stopping too early or continuing too long. In addition we shall consider when the results of one trial should stop other trials that are underway or planned to start.

Decision rules for stopping the trial

Table 12-1 summarises the general format of stopping rules. The table assumes that interim analyses are performed at predetermined intervals
Table 12-1. Decision rules for stopping a long-term trial with morbidity or mortality as an end point.

RULE 1
A statistically significant increase in a serious adverse effect is observed in an actively treated group. Minimum adverse effect rate exceeded.

RULE 2
A statistically significant decrease in morbidity or mortality is observed. Minimum benefit exceeded.

plus
A reduction in total morbidity and mortality is observed commensurate with there being no transfer of morbidity or mortality from one cause (the end point of the trial) to another.

RULE 3
The predetermined number of patients has been admitted to the trial and followed for a given length of time.

RULE 4
The number of patients recruited will not be adequate or the effect of treatment is not as great as expected.

RULE 5
Evidence accrues from other sources that make it unethical to proceed.

and that the level of significance is adjusted for repeated looks (chapter 6).

Rule 1 states that the trial must be terminated if a statistically significant and biologically important adverse effect of treatment is demonstrated. Biological importance will be determined from the severity of the adverse effect and its frequency. Rule 2 states that a trial must be designed to terminate when any one important benefit is demonstrated provided the effect is compatible with an overall benefit to the patients. A reduction in total mortality and morbidity must be apparent, although probably not statistically significant. A treatment may reduce, say, myocardial infarction or stroke yet produce an excess of other serious morbidity or mortal events. An antihypertensive drug may reduce stroke events but produce episodes of hypotension and an excess