**Statistical Standards for Protocols and Protocol Deviations**

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**Introduction**

Any pharmaceutical company involved in drug research in a major way is likely to develop internal standards for its clinical trial work. This is particularly so as the number of staff increases because of the need to control standards and to maintain consistent approaches. Statistical work is no exception, whether concerned with the design or the analysis of clinical trials.

Within ICI, the statisticians are in the process of developing a series of written guidelines for the statistical aspects of clinical trial work. The first two topics tackled have been ‘The Protocol’ and ‘Protocol Deviations’, and preliminary drafts of these have been produced. They are presented here not as polished finished articles, but as working documents which will undoubtedly develop further with experience.

**The Protocol**

The protocol of a clinical trial normally contains two sections which are the specific responsibility of the appropriate statistician: (a) the justification of the number of patients, and (b) the proposed methods of statistical analysis.

Under special circumstances the statistician also writes sections on the following topics: (c) the justification of the experimental design, (d) randomisation, and (e) the justification of certain inclusion/exclusion criteria.

**Justification of the Number of Patients**

A statistical justification of the number of patients is provided unless adequate reasons exist as to why this is not possible or appropriate. These reasons should be stated. The justification normally states the following:

* I am happy to acknowledge the input of my statistical colleagues within ICI and in particular that of S.H. Ellis, who had a major influence on the topic of protocol deviations.
1. The relevant primary end point
2. The main treatment comparison of interest
3. The assumed control mean or rate
4. The treatment effect to be detected
5. The estimated underlying variability
6. The values of type-I and type-II errors

Any nonstandard methodology is described in more detail, if necessary in an appendix. Detailed explorations of power curves should also appear in an appendix.

If a trial is designated to detect 'no difference', a minimum difference which it would be important to detect should be used in power calculations.

If plausible assumptions for the relevant control and treated results cannot be made, then the following actions are possible:

1. Base power calculations on a simpler end point, e.g. percentage response rate
2. Use trial to assess required numbers in future work
3. Carry out interim analysis to assess required trial size

In general, the level of $\alpha$ should reflect the prior probability of the hypothesis to be tested. The level of $\beta$ should reflect the probability of ever replicating the trial, or the importance of getting a definitive result with this trial alone.

It may be necessary to allow for a proportion of patients who will not complete the trial, and if so, this should be stated.

If there are several primary end points, the number of patients should be adequate to satisfy the most stringent requirement.

Trials with inadequate power should be undertaken only if there are plans to combine the results with those from other trials to achieve adequate power, or if it can be shown that the information gained from such a trial will have a clear purpose irrespective of power considerations.

The following is an example of the justification of patient numbers:

Example 1. It is hoped that the addition of treatment X to treatment A will produce a minimum further fall in diastolic blood pressure of 5 mmHg, and this is the minimum difference this trial is aiming to detect. Based on the relevant estimate of variability from an earlier trial (residual within patient sd of 8 mmHg, Bloggs and Bloggs, ICI 065432/0010, data on file), power calculations show that about 20 patients will be required in this crossover trial ($\alpha=0.05$, $\beta=0.1$). The planned size of 24 patients will allow for patients who do not complete the trial.

A simple statement to cover the situation when patient numbers cannot be justified might be as follow:

Example 2. This is the first hospital trial of ICI 123,546 in which ear-lobe distension has been measured as the primary end point. No reliable data exist on which to base estimates of patient numbers, either in the literature or in earlier studies of ICI 123,546. The trial size is therefore based on feasibility, and its adequacy will be assessed at the time of analysis.