Chapter 15
Setting the Ideal Method

15.1 Introduction

Designing a clinical study involves narrowing a topic of interest into a single focused research question, with particular attention paid to the methods used to answer the research question from a cost, viability and overall effectiveness standpoint. Once we have a fairly well-defined research question, we need to consider the best strategy to address these questions. Further considerations in clinical research, such as the clinical setting, study design, selection criteria, data collection and analysis, are influenced by the disease characteristics, prevalence, time availability, expertise, research grants and several other factors [1].

15.2 Setting

One of the first steps in a clinical study is choosing an appropriate setting in which to conduct the study (i.e. hospital, population based). Some diseases, such as migraine, may have a

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different profile when evaluated in the population than when evaluated in a hospital. On the other hand, acute diseases such as meningitis would have a similar profile in the hospital and in the community. The observations in a study may or may not be generalisable, depending on how closely the sample represents the population at large [1].

Both De Gans et al. [2] and Scarborough et al. [3] looked at the effect of adjunctive dexamethasone in bacterial meningitis. Both studies are good examples of using a hospital setting. Because the studies involved acute conditions, they utilised the fact that sicker patients will seek hospital care, to concentrate their ability to find patients with meningitis. By the same logic, it would be inappropriate to study less acute conditions in such a fashion as it would bias the study towards sicker patients.

If the sample were to be restricted to a particular age group, sex, socioeconomic background or stage of the disease, the results would be applicable to that particular group only. Hence, it is important to decide how a sample is selected. After choosing an appropriate setting, attention must be turned to the inclusion and exclusion criteria. These are often locale specific. If we compare the exclusion criteria for the two meningitis studies mentioned above, we see that in the study by de Gans [2], patients with shunts, prior neurosurgery and active tuberculosis were specifically excluded; in the Scarborough study, however, such considerations did not apply, as the locale was considerably different (sub-Saharan Africa vs. Europe) [1].

15.3 Validity (Precision) and Reliability (Consistency)

Clinical research generally requires making use of an existing test or instrument. These instruments and investigations have usually been well validated in the past, although the populations in which

such validations were conducted may be different. Many such questionnaires and patient self-rating scales (MMSE or QOLIE, for instance) were developed in another part of the world. Therefore, to use these tests in clinical studies locally, they require validation. Socio-demographic characteristics and language differences often influence such tests considerably. For example, consider a scale that uses the ability to drive a motor car as a 'quality of life' measure. Does this measure have the same relevance in India, where only a small minority of people drive their own vehicles, as it does in the USA? Hence, it is very important to ensure that the instruments that we use have good validity [1].

Validity is the degree to which the investigative goals are measured accurately. The degree to which the research truly measures what it intended to measure [4] determines the fundamentals of medical research. Another measurement issue is reliability. Reliability refers to the extent to which the research measure is a consistent and dependable indicator of medical investigation. In measurement, reliability is an estimate of the degree to which a scale measures a construct consistently when it is used under the same conditions with the same or different subjects. Reliability (consistency) describes the extent to which a measuring technique consistently provides the same results if the measurement is repeated. The validity (accuracy) of a measuring instrument is high if it measures exactly what it is supposed to measure. Thus, the validity and reliability together determine the accuracy of the measurement, which is essential to make a valid statistical inference from medical research [1].

15.4 Types of Study Design

There are many different types of study, and each has merits in particular situations [5]. In a prospective study, subjects are selected from a population and analysed for a defined future

outcome. In contrast, a retrospective study is an analysis of existing data. A study is said to be experimental if the effect of an intervention (e.g. a drug treatment or exercise programme) is investigated; otherwise, it is an observational study. A study is described as cross sectional if measurements are made at only one time point, while a longitudinal study analyses multiple time points. An analytical study is one in which the aim is to analyse the data gathered to make an inference about the effect of an intervention on an outcome variable. In a descriptive study, the data are summarised using descriptive statistics (e.g. measures of centre and spread, frequencies) without consideration of the effects of one or more of the variables on the others [6].

One of the most widely known designs is the RCT. A sample of subjects is selected from the population and allocated randomly to one of two or more groups (or arms) of the trial. One of the treatments is a control, which could be an existing treatment, a placebo or no treatment. Wherever possible, trials should be double blinded such that both the subjects and the researchers are unaware of the treatment allocations. However, although ideal, this may be impossible, for example, when one of the treatments is counselling and the other is a drug therapy [6].

A parallel group design is an RCT in which subjects are allocated randomly to either the treatment or the control group. By allocating subjects completely randomly, the expectation is that any known or unknown factors that could affect the outcome – other than the treatment(s) – will be equally distributed between each arm of the trial. However, this does not necessarily prove to be the case, and one way of dealing with this is to use a matched design [8] in which the subjects in each arm are matched for the factors known to affect the response to the treatment (e.g. age, BMI) [6].

Further efficiency can be achieved by using a within-subjects design, in which individuals are allocated to both arms of the

trial (simultaneously or consecutively). As a result, the intersubject variability is eliminated because each subject acts as his/her own control. Interventions that can be applied simultaneously include topical treatments applied to each leg. If treatments are consecutive (e.g. the comparison of two drugs to relieve chronic pain), care should be taken to avoid a carry-over effect between treatments by allowing a washout period. In addition, the order in which treatments are applied should be randomised to avoid any order effects [6].

Cross-sectional studies provide information about a population of interest at a particular moment in time. Examples include surveys to estimate the prevalence of a disease and studies to investigate the reliability of a measuring instrument [6].

15.5 Identifying Risk Factors

There are two primary ways of assessing risk factors for various diseases: prospective cohort and retrospective case-control studies. In a prospective cohort study, a group of healthy individuals is monitored until they develop the disease under investigation. These studies tend to be long, large and, therefore, expensive but provide the most reliable results. Case-control studies involve comparing subjects with the disease (cases) with individuals who do not have the disease (controls) but who are, otherwise, similar (e.g. same gender, age, co-morbidities, etc.). These are shorter studies and less expensive but less reliable than prospective cohort studies. Despite its shortcomings, this type of design has generated some important findings, most notably the association between tobacco smoking and lung cancer, found by Professor Richard Doll and his team [7].

15.6 Compliance

Compliance, or a lack of it, is one of the hazards of clinical studies: patients do not always follow the instructions they are given. This is especially likely if the intervention is inconvenient or unpleasant. There are two approaches to the subsequent analysis of the data: per ITT or PP, sometimes referred to as modified ITT. In the former, data are analysed according to what the plan and intention stated, and, in the latter, patients who do not adhere to the protocol are omitted from the analysis. For example, suppose there are two arms of a trial in which Group 1 follows a low-fat diet and walk for 20 min each day and Group 2 follows a low-fat diet plan. If a patient in Group 1 follows the diet but does not exercise, then in the ITT analysis the patient would be included in Group 1, whereas the PP analysis would exclude him/her from the analysis. There are some repercussions that can arise with PP analyses [8], and many statisticians prefer the ITT option [9].

15.7 Data Storage and Collection

Unless data are accurate, valid and reliable, the results of a medical research study will be unreliable. Security, including the protection of patient-identifiable data, is of critical importance when dealing with clinical information. Many institutions have a specialised unit that coordinates the collection, storage and management of research data, and this is the preferred option [6].

15.8 Analysis

Details of the analyses to be undertaken and the statistical tools to be used should be specified in the study plan. This will be the subject of a subsequent article [6].

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