Chapter 5
Planning Clinical Research

5.1 Introduction

To achieve their objectives, clinical trials should be designed, conducted and analysed according to sound scientific principles and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated [1].

5.2 Methodology

5.2.1 Considerations for the Plan

5.2.1.1 Non-clinical Studies

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials include duration and total exposure proposed in individual

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patients, characteristics of the drug (e.g. long half-life, biotechnology products), disease or condition targeted for treatment, use in special populations (e.g. women of childbearing potential) and route of administration. The need for non-clinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents [1].

Safety Studies

'For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (ICH M3). Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about the physiological and toxicological effects of a new drug [1]'.

Pharmacological and Pharmacokinetic Studies

'The basis and direction of the clinical exploration and development rests on the nonclinical pharmacokinetic and pharmacology profiles, which include information such as the pharmacological basis of principal effects (mechanism of action); dose-response or concentration-response relationships and duration of action; study of the potential clinical routes of administration; systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses; and studies of absorption, distribution, metabolism and excretion [1]'.

5.2.1.2 Quality of Investigational Medicinal Products

'Formulations used in clinical trials should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of drug develop-

ment. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug may be tested. Links between formulations, established by bioequivalence studies or other means, are important in interpreting clinical study results across the development program [1]'.

5.2.1.3 Phases of Clinical Development

'Clinical drug development is often described as consisting of four temporal phases (phases I–IV). It is important to recognise that the phase of development provides an inadequate basis for the classification of clinical trials because one type of trial may occur in several phases, and that the phase concept is a description, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies as for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during phase I, many such studies are conducted at each of the other three stages so they are sometimes labelled, nonetheless, as phase-I studies [1]'.

5.2.1.4 Special Considerations

'A number of special circumstances and populations require consideration on their own when they are part of the development plan [1]'.

Studies of Drug Metabolites

'Major active metabolite(s) should be identified and deserve detailed pharmacokinetic study. Timing of the metabolic assessment studies within the development plan depends on the characteristics of the individual drug [1]'.

Drug-Drug Interactions

'If a potential for drug-drug interaction is suggested by the metabolic profile, the results of non-clinical studies or information on similar drugs, studies on drug interaction during clinical development are highly recommended. For drugs that are frequently co-administered it is usually important that drug-drug interaction studies be performed in non-clinical and, if appropriate, in human studies. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (ICH E7), or whose metabolism or excretion can be altered by the effects of other drugs [1]'.

Special Populations

'Some groups in the general population may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of the dose or schedule of a drug, as compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion. Other ICH documents address such issues for geriatric patients (ICH E7) and patients from different ethnic groups (ICH E5). The need for non-clinical safety studies to support human clinical trials in special populations is addressed in the ICH M3 document [1]'.

Investigations in Pregnant Women

'In general, pregnant women should be excluded from clinical trials when the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluations of the pregnancy, foetus, and child

are very important. Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus, and child is very important [1]'.

Investigations in Nursing Women

'Excretion of the drug or its metabolites into human milk should be examined when applicable. When nursing mothers are enrolled in clinical studies, their babies should be monitored for the effects of the drug [1]'.

Investigations in Children

'The extent of the studies needed depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Some drugs may be used in children from the early stages of drug development (ICH M3)'.

'For a drug expected to be used in children, evaluation should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants [1]'.

5.2.2 Planning a Study

The main steps involved in planning a study are listed below [2]:

- Aim(s)
- Population
- Interventions
- Outcomes
- Data collection: measuring outcomes (when, by whom, how, to what level of accuracy)

- Confounding factors
- Inclusion and exclusion criteria
- Sampling strategy
- Study design
- Sample size
- Compliance
- Data storage and management
- Analysis

5.2.2.1 Aims

The first step in planning a study is to identify a clear, achievable and ethical aim. All studies need to have a purpose and aim to develop knowledge or understanding in a particular area [2].

5.2.2.2 Identifying the Population

This is the set of patients about whom we wish to make an inference. Identifying the population is not always straightforward. For example, will patients with DM (A5) include type 1, type 2, gestational, MODY, LADA, type 3, type 1.5, etc.? These different groups are likely to differ with regard to, for example, age, drug treatment and co-morbidities, and this heterogeneity would complicate an investigation [2].

5.2.2.3 Defining Interventions

An intervention is any action that is performed on the subject, or to his or her environment. This can include, for example, a drug treatment (including placebo), surgery, wearing a support device, counselling or a combination of two or more treatments [2].

5.2.2.4 Identifying the Outcome

Outcomes are endpoints or measures of the response to an intervention. The natural history of a disease such as DMD could be described by the different aids required (such as limb supports and a wheelchair), drug therapies and the time to these events. The occurrence, severity and time of onset of complications such as chest infection and osteoporosis would also be of interest [2].

5.2.2.5 Data Collection: Measuring Outcomes

There are several issues to consider when measuring an outcome. How will it be measured? When will it be measured and by whom? What is the level of accuracy and how valid and reliable is the measurement of the outcome? How will it be recorded and the data stored? Who will take responsibility for data management? These are particularly important matters when data are collected by more than one person and/or at more than one site.

Wherever possible, data should be measured and recorded as accurately as possible. It is tempting to group observations but this can be misleading and limiting. Suppose, for example, a researcher wishes to test his hypothesis that high heel height leads to back pain. Should he classify heels simply as 'high' and 'not high', as 'high', 'medium' and 'low' or as something else? Ideally, shoe heel height should be measured with a tape measure, at the back of the heel, and recorded in millimetres. Judgements such as high and low are subjective: someone who regularly wears flat shoes might regard 30 mm to be a high heel, whereas a stiletto-heel wearer might regard this as low [2].

5.2.2.6 Confounding Factors

Variables that are related to both the outcome of a study and the intervention can distort the effect of the intervention. These are known as confounding factors [3]. It is important to identify any such confounding factors during the planning phase and include them as independent variables [2].

5.2.2.7 Inclusion and Exclusion Criteria

As the names suggest, inclusion and exclusion criteria identify who will be included or excluded from the sample. Patients who could benefit from the intervention are described by the inclusion criteria. Those for whom the intervention is inappropriate or could be dangerous, or who have co-morbidities that could mask its effect, are identified by the exclusion criteria [2].

5.2.2.8 Sampling a Population

Sampling is a vital step in any research and governs any inferences that can be made. Often it is either not possible or not practical to select a random sample (e.g. if the population cannot be enumerated). In such cases, a clinician might choose to study a sample of patients in his/her clinic. Even if this sample itself is selected randomly, this does not constitute a truly random sample of the population; it is a random sample of a subset of the population that has not itself been chosen randomly. Such selections are referred to as convenience samples [2].

5.2.2.9 Types of Study Design

In a prospective study, subjects are selected from a population and analysed for a defined future outcome. In contrast, a ret-

rospective study is an analysis of existing data. A study is said to be experimental if the effect of an intervention is to be investigated (e.g. a drug treatment or exercise programme); 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 in order 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.

One of the most widely known designs is the randomised controlled trial (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 [2].

5.2.2.10 Identifying Risk Factors

Some of the most commonly reported studies involve identifying risk factors for disease. It would be unethical to deliberately subject individuals to something that could be harmful, although instances have been known. There are thus 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 tend to be long, large and therefore expensive studies, but they 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 [2].

5.2.2.11 Sample Size

Another question frequently asked is how many subjects are needed in a study. The sample size required for a study increases according to the variability of the data. Estimates of the likely variability of data can be obtained either from existing literature or by carrying out a pilot study that tests the feasibility of the main experiment and provides useful information about measures of centre and spread. Second, there is the effect size. This is a measure of the size and direction of the effect of a treatment (intervention). For continuous outcomes, this is usually expressed as a proportion of the standard deviation (SD) of the response: that is to say, it is calculated as (change in outcome with treatment, change in outcome with control) ÷ SD. This removes the effect of scale and allows comparisons to be made between different studies. When the outcome is binary (e.g. did the patient develop a hospital-acquired infection: Yes/No), one measure of effect size is the number of subjects who would need to be treated to prevent one outcome (e.g. the occurrence of one infection), and this is known as the 'number needed to treat'. Another measure of effect size in studies with binary outcomes is the odds ratio. This is the ratio of the odds of the outcome observed with one treatment divided by the odds observed with another, e.g. the odds of survival to 1 year with two regimes of chemotherapy in patients with pancreatic cancer. Provision should also be made for patients who drop out of the study [2].

5.2.2.12 Compliance

Compliance, or 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 intention to treat (ITT) or per protocol (PP, sometimes referred to as modified ITT). In the former, data are analysed according to the stated intention (plan), and in the latter, patients who do not adhere to the protocol are omitted from the analysis [2].

5.2.2.13 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 [2].

5.2.2.14 Analysis

Details of the analyses to be undertaken and the statistical tools to be used should be specified in the study plan [2].

References

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