



**UKCCSG:**  
**AN INTRODUCTION TO CLINICAL TRIALS**

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## Introduction

Traditional medical practice entails a doctor prescribing for a patient that treatment which in his judgement, based on past experience of himself and others, offers the best prognosis. Since there are few conditions for which treatment is 100% effective, there is much scope for potential improvements in therapy. Such improvements are derived via a clinical trial.

## What is a Clinical Trial?

Any planned experiment which involves patients and is designed to reveal the most appropriate treatment of future patients with a given medical condition. It uses results based on a limited sample of patients to make inferences about how treatment should be conducted in the general population of patients who will require treatment in the future.

The majority of clinical trials are concerned with the evaluation of drug therapy, but they can also be concerned with other forms of treatment, eg surgical procedures, radiotherapy, etc., or quality of life, etc.

Clinical trials fall into 4 phases:

- Phase I - to determine an acceptable drug dosage
- Phase II - to provide evidence of efficacy of treatment
- Phase III - to compare efficacy/side effects with those of other drugs/treatments/placebo
- Phase IV - large scale epidemiological study (mainly industry)

### Phase I Trials

Phase I trials can be seen as toxicity screening studies where, after testing in the laboratory and on animals, a new drug is administered for the first time in man in order to determine the maximum tolerated dose. (Of the many new drugs manufactured, only a very small number actually get to this stage). There are usually two aims of a phase I trial - to establish optimal dose to be used in a phase II trial for drug efficacy, and to determine the type and degree of toxicity (adverse effects) associated with the drug. Dose limiting toxicity (DLT) is the point at which an unacceptable level of toxicity is identified. The dose level below that at which DLT is identified in 2 of a maximum of 6 patients is known as the maximum tolerated dose (MTD), ie the optimal dose to be taken forward to a phase II study. Because of their complexity, phase I trials only take place in UKCCSG centres which fulfil the specific requirements for Phase I studies. Patients entering Phase I trials will have failed on conventional therapy.

### Phase II Trials

After determining the recommended dose in a limited number of patients in Phase I trials, new drugs are subjected in Phase II trials to their initial screen in man for possible anti-tumour activity. The goal of a Phase II trial is thus to identify in a small number of patients those drugs of potential promise for more intensive testing in a given population or tumour type. The endpoints of such a trial are response rate and toxicity.

### **Phase III Trials**

After a drug is found to have at least some minimal amount of anti-tumour activity in Phase II trials, the next step is to determine its relative efficacy in a larger Phase III trial. Here the drug will be compared, either alone, or in combination with other drugs, to a control group, usually the best available treatment, or a historical control.

Most UKCCSG trials are Phase III, comparing patients on a new treatment versus standard treatment, to try and establish whether treatment A is better than treatment B.

### **Clinical Trial procedure**

In conducting a clinical trial a number of steps have to be followed:

- Define the purpose of the trial
- Design the trial (including writing the protocol and forms)
- Conduct the trial
- Analyse the data
- Draw conclusions: publish results.

### **The role of the Chief Investigator**

For multi-centre trials there will be a designated Chief Investigator or lead Clinician. Prior to commencement of a trial, the Chief Investigator is responsible for preparation of the protocol. During the conduct of the study he/she is in charge of medical monitoring (particularly toxicity/safety) and, finally, on completion of the study he is responsible for liaison with statisticians over analysis, and finally for reporting the results.

### **The Protocol**

This states all the information relating to purpose, design and conduct of the trial. It defines which patients are eligible; which treatments are to be evaluated; how each patient's response is to be assessed; the end point for evaluating treatment and how the study will be coordinated.

Main features of a Protocol are:

Background and general aims; specific objectives; patient selection (inclusion and exclusion) criteria; diagnostic tests; treatment schedules; methods of patient response evaluation; trial design; arrangements for registration and, where appropriate, randomisation of patients; required size of study; monitoring of trial progress; forms and data handling; protocol deviations; plans for statistical analysis; administrative responsibilities; patient information sheets and consent forms.

### **How is the size of a clinical trial determined?**

'How many patients do we need?' is the fundamental question. Statistical methods can be used to determine the number of patients required to meet the trial's principal

objectives but practical matters such as availability of patients and resources must also be taken into account. The estimated time period for patient accrual to any trial will depend on the frequency of a given disease.

### **What is a multi-centre trial?**

With a comparatively rare disease, it would not be feasible to accrue sufficient numbers of patients to conduct a trial in a single centre. Hence the need for multi-centre trials, such as are conducted within UKCCSG, and these may be national or international.

Multi-centre trials have the advantage that patient accrual is quicker so that the trial can be made larger and/or the intended size is reached more quickly. The end result should be that a multi-centre trial reaches more reliable conclusions at a faster rate so that overall progress in the treatment of a disease is enhanced. By involving patients from several centres, any conclusions have a broader more representative base than can be reached in a single centre. The conduct of multi-centre trials has implications for: complex administration and planning; expensive so need to ensure adequate funding; need for good communication and standardisation between all participants.

### **Role of coordinating centre/Trials Unit**

In multi-centre trials, the coordinating centre (or Trials Unit) has a vital role in registration and randomisation of patients, collecting and processing patient records, dealing with enquiries, monitoring toxicity, and providing feedback. In addition the Trials Unit will work with Chief Investigators to ensure compliance with the increasing number of regulatory needs.

### **What is randomisation?**

To avoid the risk of biased results, a patient can be randomly assigned to a form of treatment. This is essential in guaranteeing that there is no bias in the selection of patients for the different treatments but it must be properly conducted. The result of the two arms are kept blinded from participating clinicians while the study is ongoing, and will not be revealed until the end of the study.

It is not always possible to conduct randomised trials in paediatric oncology because of the rarity of the tumours, and the small numbers of available patients. In practice about one third of all UKCCSG trials will be randomised. The conduct of all is subject to close scrutiny by Independent Data Monitoring Committees.

### **How is a patient randomised for a particular trial?**

For each patient who might be considered suitable for inclusion in a clinical trial, the following sequence of events should take place:

- patient diagnosed for treatment;
- patient defined as eligible for inclusion in trial (according to Protocol);
- clinician is willing to accept randomisation;
- patient consent (or that of parent) is obtained;
- patient formally entered on trial;

- treatment assignment obtained from randomisation list (prepared by independent statistician and generated by computer);
- on study forms are completed
- treatment commences.

Patient registration and randomisation must be achieved promptly so that there is no delay in the commencement of treatment.

### **What is a control in clinical trials?**

A control is a patient who receives a treatment used for comparison with the study drug or treatment.

### **Forms and data management**

The need for accurate recording and processing of patient data is fundamental to any clinical trial. If data stored on the master data file are incorrect, conclusions of the analyses will also inevitably be incorrect. While collecting and handling data, it is necessary to keep in mind that only accuracy, correctness and completeness of the data collected, as well as timely form return, will lead to the reporting of valid results. The main purpose of having well designed forms is so that patient evaluations can be made suitable for statistical analysis. But before such analysis can take place all data have to be collected, processed and checked. Efficient data management thus becomes a priority. The checking process is ongoing throughout the duration of a trial. With multi-centre trials the whole process of data collection and resolution of queries becomes easier if each centre has an on-site data manager. There is a need for close collaboration between Chief Investigator and Data Centre personnel in form design, and with on-site data managers in training in form completion.

All forms should be returned in a timely manner according to the Schedule of Form Return in the Protocol. This is particularly so with Serious Adverse Event Forms, where Centres must report SAEs within 24 hours of knowledge of the event. This is essential for 'real time' safety monitoring of the trial.

### **Statistics in clinical trials**

Statistics play an essential part throughout any clinical trial, from planning, conduct, interim analysis and final analysis and reporting. The statistician devises the randomisation schedules. Advice on sample size; criteria for measuring treatment differences and analysis of response rates are all the responsibility of the statistician. Time to an event of interest is often used as an endpoint for evaluation of therapies in clinical trials. Time to recurrence of disease, duration of complete remission, and overall survival are examples. The data are shown in the form of survival curves. Analysis (interim and final) are the responsibility of the study statistician. The statistician will also be the link for a trial with the Independent Data Monitoring Committee.

### **The role of the Trial Coordinator**

It is the trial coordinator in the Trials Unit who is responsible for a trial in terms of data collection and conduct of administrative matters relating to that trial. When a

new trial is being set up the trial coordinator, through experience in the necessity for attention to detail, should be able to see whether all terms used in the protocol are precisely defined, if definitions are clear enough, if frequency of follow up is defined, etc. The trial coordinator should also design/review any new forms to ensure that they are clear, easy to complete, contain all the relevant information, and do not contain unnecessary information.

Once the trial is up and running the Trial Coordinator will be the focal point for all aspects of trial conduct (form return, resolution of queries, data checking, data entry, generation of reports, follow up etc).

## **Follow up**

Many trials of serious illness are conducted to see if a treatment can prevent or delay the occurrence of a major event (eg death, recurrence of cancer, etc.). Such studies usually require long-term follow up. Even when a trial is closed to patient entry (ie when the required number of patients have been recruited), follow up continues.

In trials of childhood cancer, where many children are now surviving many years after treatment, follow up in the centre is carried out indefinitely in order to assess the long-term effects, if any, of treatment. Routine collection of follow up data by the trials unit will usually continue for a defined period (ie 10 years). After that time period it is more likely that specific late effects studies will be conducted in a particular patient population.

## **How is trial data analysed/evaluated?**

Data analysis is complex but may be used to show, for example, survival data. For clinical trials into potentially fatal diseases, eg cancer, the main evaluation of patient outcome is whether the patient dies or not, and the time from entry into the trial until death. Alternatively, patient outcome may be the time to some other measure of patient relapse, ie disease recurrence. According to the specific requirements of the trial protocol, both interim and final analysis may be carried out.

## **What are pharmacokinetic studies?**

These are studies designed to identify and describe one or more of the following basic pharmacological concepts in humans: absorption; distribution; metabolism and excretion, of drugs. These may be either stand alone studies, or incorporated into main clinical protocols. UKCCSG Centres wishing to participate in pharmacokinetic studies will need to have a research nurse in post, as it is the research nurse who is involved in sampling and form completion for these studies.

## **Ethical issues**

Every clinical trial requires careful assessment of whether it is ethically acceptable for patients to participate. Ethical considerations should be of continuing concern throughout the design and conduct of the trial. For the conduct of clinical trials in the UK, there is a very thorough process of both national and local Ethical Committee approval, designed to ensure protection of the patient. All clinical trials need to have

their protocol approved by such a committee before the trial commences. The ethical committee approval places considerable emphasis on informed patient, or parent, consent.

The safety and wellbeing of the patient are paramount and must always take precedence over science and research.

## **Conduct of Clinical Trials/Research**

Recommendations guiding medical doctors in biomedical research involving human subjects are contained in the Declaration of Helsinki, adopted by the World Medical Assembly in Helsinki in 1964, and updated subsequently.

Originally introduced in connection with pharmaceutical company trials the principles of Good Clinical Practice have now been adopted (to a greater or lesser degree) by all conducting clinical trials (ie both pharmaceutical companies and academia). The EU Directive on GCP in Clinical Trials, aimed at standardising trial conduct throughout Europe and effective from 1st May 2004, brings an increasing level of regulatory requirements to the conduct of clinical trials, and represents the biggest single challenge faced by those working in the area of clinical trials.

## **What is a blind trial?**

In any randomised trial the comparison of treatments may be distorted if the patient himself and those responsible for treatment and evaluation know which treatment is being used. A blind trial is one where the patient does not know whether he is receiving the active drug or a placebo. A double blind trial is one where neither patient nor clinician know which treatment is being given. Use of placebo trials in paediatric oncology is extremely rare.

## **Interpretation and publication of findings**

The purpose of clinical trials is to advance knowledge about the treatment of a disease and hence cure more patients. The reporting and interpretation of trial results is a major issue as the publication in a referred journal is the most effective way to inform investigators of the advances of current research (in Journals such as 'Cancer', or in the form of presentations at Scientific Meetings).

## **Survival Curves**

The information on effectiveness of treatment of children in trials is best illustrated by survival curves. Survival most commonly refers to the time from diagnosis of disease (entry to trial) until death. It may also be from diagnosis to relapse of the disease or death (event free survival), or from remission to relapse (disease free survival).

At any moment, when analysis of the data is carried out a large proportion of patients will hopefully still be alive and in remission. They can be included in the analysis, and their data is as important as that of relapsing patients. This data is termed 'censored', meaning their time to relapse or death is unknown but must be longer than the last reported time they were alive.

The commonly used method to calculate the best estimate of survival at any time from diagnosis or remission is the "actuarial" (also known as "Kaplan-Meier" or "Product limit") method.

The essential calculation is:

Estimated % surviving beyond time T =

$$\frac{\text{no. of patients surviving beyond T}}{\text{(no. surviving beyond T + no. dying at T)}} \times \text{estimated \% surviving up to time T}$$

This calculation is made after each event. The data are then presented as a series of steps, with a drop at each event time. This provides curves which will not differ systematically from the final curve, calculated when all patients have full follow up.

The shapes of the curves can vary greatly. Clearly the curves cannot climb upwards, but some drop earlier than others and flatten out sooner. This reflects the type and stage of disease, as well as the course of disease.

Comparisons between curves can be made for groups of patients either given different treatments (as in randomised trials) or with different characteristics when initially diagnosed (prognostic factors). A statistical test may be carried out to assess the evidence for any difference. A common test is the log rank test, which is more sensitive to later events than other tests.

### **UKCCSG Protocols – development and approval process**

For UKCCSG protocols there is a two stage process for approval. The day to day development of the protocol will be led by the identified Chief Investigator, in collaboration with colleagues from other disciplines within the particular Tumour Working Group.

Once the clinical ideas have been formulated to a reasonable degree, a 'concept' will be produced, using a standard template. The concept contains the basic ideas behind the proposed study, including statistical information to demonstrate that the study is viable, in terms of available patient numbers and statistical power to answer the study questions.

Once the concept has been approved at a national UKCCSG meeting, the Chief Investigator will be required to develop a draft protocol for final approval. Once that final draft has been approved, the protocol is finalised and submitted for ethical approval.

Throughout the protocol development process a number of Data Centre personnel will be involved (Trial Coordinator and Statistician, and Executive Director).

The approval process by UKCCSG involves consideration at one of the two national meetings a year. Prior to discussion at the national meeting, the concept or final draft is circulated to centres for discussion and feedback of comments. The result of that feedback is then disseminated as part of the approval discussions.

## References:

There are many books and training courses available on the subject of clinical trials. The following are recommended as good general introductions.

'Clinical Trials: A Practical Approach' by Stuart Pocock. Pub. Wiley, 1983

'Data Management and Clinical Trials: EORTC Study Group on Data Management'  
Ed. N. Rotmensch (*now out of print*)

'Cancer Clinical Trials: Method and Practice'. Ed. M.E. Buyse, M.J. Staquet and R.J. Sylvester. Pub. Oxford Medical Publications.