

# Clinical Trials in Family Practice

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## Introduction

At some stage of their careers many Family Physicians and General Practitioners will be approached by a pharmaceutical company or a 'clinical research organisation' (CRO) to be an investigator in a clinical trial. According to the South African Clinical Trials Guidelines 2000: a clinical trial is '[a]ny investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.'<sup>1</sup>

In this article, we will consider clinical trials in the South African context from the point of view of the application for review and approval as required for clinical trials. Two important authorisations are needed before a clinical trial can commence. The first of these is an ethics committee (EC) approval; the other is approval by the Medicines Control Council (MCC). (*SA Fam Pract 2003;45(4):16-19*)

### ETHICS COMMITTEE APPROVAL

A National Health Ethics Council/Committee is in the process of being established. Ethics committees will in the near future have to be accredited with this Council according to various requirements and standards. At present most of the recognised ethics committees are based in academic institutions and the rule of thumb is that for research being undertaken in one of these settings, approval should be obtained from their own ethics committee. For other settings – e.g. practice, private hospitals, etc., – approval should be sought from an independent recognised ethics committee.

### MEDICINES CONTROL COUNCIL APPROVAL

The MCC has a specially constituted committee – the Clinical Trials Committee (CTC) which reviews all clinical trial applications and makes recommendations to the MCC in terms of approving (or not approving) them.

The CTC consists of about twenty

members from all over South Africa who meet every six weeks (2003 calendar) to review the applications.

The members represent a variety of medical and pharmaceuticals disciplines. Each member is provided with copies of all applications (the application form) for a particular cycle. Individual members are requested to review a number of trials in-depth (dependent on the number submitted), and present these to the CTC. The committee then discusses the trials and makes recommendations to Council (MCC).

### THE APPLICATION 'PACKAGE'

The usual application consists of a completed clinical trial application form which can be downloaded from the internet ([http://www.pharmnet.co.za/frame\\_regservices.htm](http://www.pharmnet.co.za/frame_regservices.htm)), the protocol, an investigator's brochure and/or package inserts, investigators' CVs and signed declarations, copies of insurance certificates, and other required accompanying documents. Electronic versions of these, where applicable, should also be submitted.

### THE CLINICAL TRIAL APPLICATION FORM

Although a clinical research associate (CRA) usually completes the application, it is incumbent upon the investigators (usually represented by the 'principal' investigators) to ensure that the study is both scientifically and ethically sound, and that the application is logically completed. Many CRAs do not have scientific or clinical training and have difficulty in summarising, for example, the rationale of the study. It should be borne in mind that the individual reviewers of the application focus on the application form as submitted by the applicant (represented by the CRO or CRA), and use the supporting documentation to double check on the information presented in the application.

#### *The application form has three sections:*

- Section 1 lists the required documentation and includes some details of the substances to be tested (e.g. MCC registration number of a medicine, if applicable)

- Section 2 provides administrative and supplementary details (such as contact details of all sites and for all the investigators). An interesting aspect of this section is the request for details of investigator's time commitments – some investigators claim to work 168 hours a week, although the form states that this is the denominator for determining the different percentages!
- Section 3 summarises important components of the clinical trial itself. This summary forms the applicant's report to the CTC and is the most important component of the application. These will be dealt with below on a point by point basis.

#### Title

The title of the study should be as complete as possible. The major components of the study should be included (blinding, randomisation, placebo, phase etc.) Also the intention of the study should be clear from the title: is it primarily to test safety or efficacy, or both; or is it a comparison of existing therapies. The nature of the therapy should be clear – for example, where an anti-asthma medication is being used in addition to 'usual' therapy, the title should indicate that it is 'adjunctive' therapy. One of the reasons for this is that the title of the study should be the same as the title under which the study is eventually published, and this becomes particularly important in terms of doing 'searches' of study databases.

#### Rationale (summarised)

Here it is important to indicate the reasons for the study being done at all, and particularly why it should be done in South Africa. Completion of this section should probably not (in most cases) be left solely to a CRA.

#### Background information

This should include essential points only for most, if not all, of the following:

- Disease / problem.
- South African context (e.g. local epidemiology).
- Properties of Drug / Entity; hypotheses about mechanism of action, etc.
- Pre-clinical findings: (e.g. labora-

tory/animal/toxicity/mutagenicity).

- Clinical findings (e.g. phases; pharmacokinetics; pharmacodynamics; dose-finding studies; adverse drug reactions, number needed to treat/harm [NNT/NNH], other relevant information).
- Systematic review(s) and/or citations per year-group on a Medline search.

#### Objectives of study

Most studies have primary objectives and secondary objectives. These should not only be listed, but each one should be justified with an explanatory phrase or sentence. The objectives should be scientifically credible. Each objective should be included in the data analysis (the statistics section of the protocol should provide the details). Again – most CRAs will be able to list the objectives very easily, but they may need help with the justification.

#### Study design

This needs to be clearly described and each component justified; for example: the phase, the use of placebo; the dosages; the randomisation methodology; the blinding mechanism; the duration of the study; etc. Another particularly important aspect to be considered in terms of the study design is whether or not it will actually provide the information listed in the objectives. Again, although most CRAs will be able to rattle off the components of the study design, they may not have the training to be able to justify them.

#### Participants

The proposed number of participants and how this number has been determined needs to be stated; the investigator(s) should be able to enroll the required number within the stipulated time.

#### Eligibility and enrollment

These focus on the inclusion and exclusion criteria, which should be listed and each of them justified. The inclusion criteria often focus on the 'disease' state and/or problem as well as the age limits. Exclusion criteria are those conditions in patients, which make them ineligible for the study. Again it is the justification of these criteria that is

important. For example if HIV-infected persons are to be excluded, it needs to be ensured that this is for scientific reasons and is not discriminatory. (It also implies that an HIV test has to be done, or has previously been done. Proper HIV pre- and post-test counselling will need to be in place and may need to be incorporated into the patient information leaflet and the informed consent documents.) The scientific justification for eligibility criteria should be consistent with the objectives of the trial. The enrollment procedures should also be explicit, logical and clear.

#### Treatment modalities and regimens, drug accountability

This is all about how the medication is given, which must be clearly explained in terms of route of administration, dose, etc. These should also be justified for all participant groups/arms. Drug accountability needs to be clearly described.

#### Outcome measurements/variables

These often include before and after measures, which should be clearly stated and justified. The justification may have to include the use of surrogate endpoints and the extent to which these surrogates actually can be used to represent the particular morbidity (or mortality) being investigated.

#### Adverse events

Even in 'efficacy-only' studies, adverse drug reactions and serious adverse events need to be monitored and reported. Where these are mostly already known, they should as far as possible be prevented. (For example, where a hepatotoxic effect is known, persons with liver disease should be excluded in the exclusion criteria.) The definitions being used – including causality assignment – must be listed. These definitions are usually standardised according to the particular 'Good Clinical Practice' (GCP) protocol being followed. The recording, reporting, reporting time-lines, the action(s) to be taken, should all be clearly described.

#### Statistical measures

- The determination of the sample size should be correct, clear and justified (with and/or without stratification).

- Statistical method(s) and analysis of quantitative measures should be appropriate, clear and justified.
- Statistical method(s) and analysis of qualitative measures should be appropriate, clear and justified.
- Data processing (how, where, when, who) should be clearly described and justified.
- If an 'interim analysis' is envisaged, and there are reasons for stopping a trial (e.g. unexpected serious adverse drug reactions) the 'stopping rules' should clearly be stated. If an interim analysis is not envisaged this should be justified.

Most CRAs and indeed most investigators will not have the skills to justify the different statistical measures being used. These justifications may not even appear in the protocol. The CTC has its own biostatistician to advise it.

#### Ethical Issues

Some of the ethical issues, which should be addressed include:

- Explanation of which GCP guidelines are being followed. Clinical trials in South Africa should abide by and adhere to the South African Guidelines.<sup>1</sup> Particular attention should be paid to the Helsinki Declaration 2000 – and where difficulties in adhering to this (e.g. justification of a placebo arm, ongoing treatment following the end of the trial) these should be stated with reasons.
  - The choice of investigators should be appropriate. The qualifications and requirements for investigators are listed in the SA Clinical Trials Guidelines 2000. Where investigators do not meet these requirements this should be made explicit and what steps will be taken to ensure that the investigator(s) concerned are properly supported and guided in carrying out the trial. (Note: The SA Clinical Trials Guidelines 2000 are in the process of being updated and a few discrepancies and areas needing clarification will be addressed.)
  - The need for, appropriateness of, and relevance of GCP training / updating for staff involved in the trial should be addressed.
- The capacity building element of the trial should be stated. Although this is not a legal 'requirement' in terms of applications, there is a moral imperative to ensure that increasing the number of researchers and widening the scope of research in South Africa is addressed.
  - The adequacy of the resources of the sites should be addressed (for example, in terms of emergency equipment and emergency training); and the resources of the sponsor must be adequate. It would not be ethical to stop a clinical trial halfway through because the sponsor has run out of sufficient funds. [A declaration to this effect must be signed and is one of the supporting documents to be submitted.]
  - The monitors and a monitoring plan need to be adequate. Very often, pharmaceutical companies will have their own standard operating procedures (SOPs) for monitoring. The ethics committees may in future be required to monitor sites for GCP, and the Inspectorate of the Medicines Regulatory Affairs is likely to be increasingly active in monitoring clinical trials in the future.
  - An indication as to how the staff apart from the investigators (e.g. monitors, pharmacists, nursing staff) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements, should be provided.
  - The details of insurance and indemnity measures should be provided and adequate. Where a particular trial is not detailed by title and protocol number on the insurance certificate because the sponsor has blanket insurance for clinical trials, an accompanying letter which includes the title and protocol number and which states that the blanket insurance does indeed apply to this particular trial should be submitted by a person authorised to make such a statement.
  - The Patient Information Leaflet (PIL) and Informed Consent should be written in appropriate language (to be understood at a Grade 8 level of education); the English version needs to be submitted and an indication of translation into other

languages as appropriate should be made; the possible benefits / risks of participating should be clear; the right to withdraw without penalty should be explicit; patient rights should not be infringed; the relevant contact details should be included; and in terms of compensation for trial injury, the statement that the ABPI guidelines will be used, and that these are available should the participant desire them, is included.)

- Separate PILs and informed consent forms for any proposed archiving of blood specimens for later research or for genetics research must be provided (and justified in the study design).
- An ethical publication policy should be incorporated as indicated in various international guidelines.
- The ongoing treatment and/or management of participants in terms of their disease condition(s) related to the clinical trial, after completion of the study, must be made explicit.
- The capacity of the ethics committee to monitor sites, if a local ethics committee has not approved the trial, should be made explicit.
- An explanation (or breakdown) of the remuneration received by the investigators, study co-ordinators, monitors, and others involved in the study should be provided. Compensation for participants should be provided in terms of their time, transport and food, where these are applicable. The possibility of perverse incentives should be considered both in terms of participants and investigators.

A recurring ethical issue is one where a clinical trial is performed in South Africa, which uses only imported medicines that will not at a later stage be registered in South Africa. There is no apparent benefit to the country apart from a financial benefit to a few people and possibly a short-term therapeutic benefit to a few participants.

#### OTHER RELEVANT INFORMATION

The person completing the application (possibly with the help of the investigator) should also ensure that the

references in the protocol are adequate and current; that there are no discrepancies between the protocol, investigator's brochure (or package inserts) and the application; and that the application covers all the relevant aspects of the study.

## CONCLUSION

One of the recurring criticisms of the MCC has been that the time-frame for review and approval takes too long. Theoretically it should take only six weeks. However, many applications are incomplete, and queries have to be sent to the applicant for clarification of issues, or because of substandard applications. Sometimes queries have to be sent to applicants more than once. Most of these situations would appear to be where a CRA has simply used a 'copy and paste' method to complete the

application without understanding the rationale and justification for the study, and where the principal investigator has not paid adequate attention to detail in her/his reading of the protocol and other documents, nor in double-checking the actual application itself.

When occasionally major problems are found in a study, which has already received ethics committee approval, major questions are raised as to the rigour with which an application was reviewed by the ethics committee. It should be remembered that the purpose of the clinical trial application is to assist members of the Clinical Trials Committee to determine the answers to the following questions in making a recommendation to the MCC:

- Does this proposed trial contribute to new knowledge in a scientific way?
- Are all aspects of this proposed trial ethical?
- Can patient safety be assured?
- Should this trial be done in South Africa?

Finally, if you are approached to participate as an investigator in a clinical trial, it would be worth ensuring that the documents submitted to the Clinical Trials Committee (which, with other investigators, bear your name and your signature) are of the requisite standard. □

### **Declaration:**

*Dr Jobson is a member of the Clinical Trials Committee of the Medicines Control Council.*

### **References**

1. Department of Health, South Africa. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa: Clinical Trials Guidelines 2000.