



Contract Research Opportunities in SA Family Practice

Obligations of the Investigator – towards the Sponsor and the Authorities

1. Introduction

It has been estimated that by 1994, the medications produced by the pharmaceutical industry over the preceding 50 years had saved more than 1.5 million lives and \$140 billion in the treatment of tuberculosis, poliomyelitis, coronary artery disease and cerebrovascular disease alone.¹ Developing these life-saving medicines is a fascinating albeit costly and time consuming process.

Medical practitioners have a valuable role to play as clinical investigators in this development process. Although participating as investigator in clinical research can be both satisfying and rewarding, it also brings with it certain obligations the investigator needs to be aware of right from the outset. Before discussing these obligations we need to have a closer look at what the development process entails.

2. Developing new medicines

A new medicine usually starts its life in a laboratory as a molecule or chemical compound identified as having potentially useful activity in the treatment, prevention or diagnosis of a disease or condition. This is followed by a rigorous program of pre-clinical experimentation designed to compile a comprehensive pharmacological profile of the molecule and to gather basic safety and toxicity information before the new medicine can be tested in man. The process of testing in man or *clinical research* can be divided into four generally recognised developmental phases.²

Phase I trials, also referred to as *first in man* trials, are initial safety trials conducted under strictly controlled circumstances in a small number of healthy male volunteers. There are two questions to be answered by these

trials, i.e. "Is the new medicine safe?" and "What are the pharmacokinetics involved?"

Phase II trials, or *first administration to patient trials*, are well-controlled trials conducted in a small number of volunteers with the disease or condition to be treated, diagnosed or prevented and are designed to answer the question: "Does the new medicine work in patients?"

Phase III trials are those trials conducted to gather additional safety and efficacy data in large patient populations for which the new medicine is eventually intended. These trials are often referred to as *pivotal* trials because they are the last step in the development process before application for marketing authorisation is made.

Phase IV trials are conducted after a medicine is marketed to gather additional information about the medicine's efficacy and safety profile. Commonly referred to as *post-marketing surveillance*, these trials provide information about previously unknown or inadequately defined adverse reactions and related risk factors under actual conditions of use in large numbers of patients.³

3. Obligations of the clinical investigator

We are going to consider the obligations of the investigator in two categories: Those toward the sponsor, i.e. pharmaceutical company developing the new medicine, and those to the authorities.

3.1 Obligations to the sponsor

The investigator's obligations toward the sponsor are best viewed from the sponsor's vantage point. The sponsor

is conducting the research to obtain data on the safety and efficacy of the medicine under development to support the eventual application for marketing authorisation. Because of the high cost of this research, it is very important that investigators who undertake to conduct a clinical trial are able to carry out the trial efficiently and within the shortest time possible.

The investigator's first obligation to the sponsor is therefore to recruit the required number of eligible subjects within the agreed recruitment period. Even before agreeing to conduct the trial, the investigator should give the sponsor an accurate estimate of the number of subjects he/she would be able to recruit. To be able to do this, the investigator needs to be fully conversant with the protocol and the proper use of the medicine under development. The inclusion and exclusion criteria specified in the protocol need to be carefully evaluated against the type of patient regularly seen in the investigator's practice, because it is vitally important that the subjects recruited for the trial meet these inclusion and exclusion criteria. Recruiting subjects who are later found to be ineligible for the trial is a waste of the sponsor's time and money.

The investigator's next obligation to the sponsor is to gather accurate and complete data. Making clear and detailed clinical notes during trial related visits is one of the most important means of generating data that is both believable and complete. Data should never be invented for tests that were missed or forgotten. Another vital requirement for ensuring the integrity of the data is strict adherence to the protocol. Deviations from the protocol are only acceptable if they are made in the interest of subject safety. The bottom line is that the sponsor needs accurate, reliable and

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trustworthy data to demonstrate or confirm the safety and efficacy of the medicine under investigation. Nothing less is acceptable.

Finally, to be able to conduct the trial efficiently, an investigator needs to have enough time and resources to perform trial related activities. Conducting a clinical trial takes up a considerable amount of time and the investigator is obligated to plan ahead and exercise strict time management in order to be available to attend to all his/her trial related duties. In addition, the conduct of a clinical trial involves a large amount of administration and documentation, and a well-trained trial co-ordinator is an indispensable resource for ensuring that all files are kept up-to-date and correspondence handled in a timely manner.

3.2 Obligations to the authorities

Because the development of new medicines is strictly regulated worldwide, any investigator who commits to conducting a clinical trial automatically incurs certain obligations to the authorities. All clinical trials have to be conducted in compliance with the Declaration of Helsinki,⁴ revised and published by the World Medical Association in 2004, Good Clinical Practice (GCP) and the applicable regulatory requirements. In South Africa all clinical trials have to be conducted in compliance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, published in 2000 by the Department of Health.⁵ We will refer to this guideline as SA GCP. Internationally the standard for conducting clinical research is the well-known Guideline for Good Clinical Practice of the International Conference on Harmonisation (ICH), commonly referred to as ICH GCP.⁶ Although largely identical to ICH GCP, the SA GCP Guideline contains some country specific requirements which take precedence over any other requirements for locally conducted trials.

The Medicines Control Council (MCC) requires any investigator who wants to participate in clinical research in South Africa to provide a certificate indicating that he/she had completed a course in GCP within the preceding three years.

Adherence to GCP implicitly implies compliance with the relevant local laws and regulations. In fact, the requirement to comply with local regulations runs like a golden thread through the text of the ICH GCP Guideline.⁶ In South Africa, the conduct of clinical trials is regulated by Act, No 101 of 1965, regulation 34.⁷

Obligations to the authorities is in effect shared by the sponsor and the investigator. Before initiating a clinical trial, the sponsor has to obtain approval from the applicable regulatory authority (MCC in South Africa) to begin the trial. The investigator on his/her part has the obligation to obtain approval from the relevant Ethics Committee (EC) for the protocol, the informed consent form and all other written information to be provided to subjects. The sponsor again, needs to obtain confirmation of EC review and approval from the investigator and must provide proof of this approval as part of the submission to the MCC. Needless to say, obtaining regulatory and ethics approval is a crucial step in the conduct of any clinical trial. The sponsor cannot supply the investigator with the medicine under investigation, nor can the investigator enrol any subjects on the trial before these two approvals have been obtained.

During the conduct of the trial, the sponsor and the investigator are also obliged keep the regulatory authority and the EC informed about the progress of the trial and any safety information that becomes available about the new medicine. The investigator is obliged to submit progress reports on the trial status to the sponsor, the MCC and the EC according to the format and frequency they require, followed by a final report upon trial completion (SA 2000, section 3.14). Safety reporting needs to be done on an ongoing basis

by both the sponsor and the investigator.

The investigator will be able to pick up safety issues at his site in the form of adverse events (AEs), serious adverse events (SAEs) and adverse drug reactions (ADRs) (see ref.6 for the definitions of these terms). Withholding or under-reporting safety information is a serious offence and can result in the MCC stopping a clinical trial.

4. Conclusion

It is understandable that the obligations discussed above may seem daunting, but in reality they represent the minimum requirements for participation in clinical research. They should not be seen as a deterrent, but rather as an invitation to meet the challenge implied. By fulfilling these obligations the investigator ensures that the conduct of the trial is a rewarding experience to all parties involved and well worth the effort invested. 🙌

References

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