

JOINT POSITION STATEMENT OF THE PHARMACEUTICAL INDUSTRY AND CLINICAL TRIAL ORGANISATIONS

ON CLINICAL TRIALS IN SOUTH AFRICA

June 2007

Introduction

Clinical trials, carried out according to international standards of Good Clinical Practice, are important for medical progress and should be encouraged in South Africa.

They contribute to scientific advances necessary to improve healthcare, including the management of diseases of particular concern in Africa and the developing world. In addition they serve as a source of direct foreign investment. Understanding the role of clinical trials, and the basic principles which underpin them is essential in order to ensure that South Africa attracts more clinical trials, and more patients benefit from participating in them.

What are clinical trials?

The purpose of a clinical trial is to investigate the safety and efficacy (effectiveness) of a medicine¹. Clinical trials are required prior to the granting of a marketing authorization for a new medicine, when the product is changed in some way (e.g. a new form of presentation), when a product is used for an unauthorized indication, or to gain further information about the authorized form².

Patient and clinical trials

Patient rights, safety (minimizing risk to patient health) and well-being are the highest priority in all clinical research and should prevail over the interests of science and society. For this reason trials are governed by a review and oversight process designed specifically to protect the rights and safety of patients who agree to participate in them.

Approval to conduct trials

Approval to conduct trials involves a rigorous, multi-layered review and oversight process. The process is specifically designed to protect the rights and safety of individuals who enrol into trials and, in South Africa, involves two independent bodies namely an Ethics Committee and the Medicines Control Council.

Ethics committees are responsible for overseeing individual clinical trials. As such, they review and approve all aspects of trials and ensure the risks are as low as possible and are outweighed by the potential benefits. Such committees are composed of both medical and non-medical persons to ensure amongst other things, that patient rights and safety are properly addressed.

In South Africa the Medicines Control Council (MCC) shares the responsibility, with the Ethics committee, for the approval and oversight of clinical trials. Specific regulations and guidelines have been established by the MCC to ensure that the study has been appropriately planned and that the safety of the trial participants has been properly addressed; these include official South African guidelines for GCP (see below) and guidelines on reporting adverse drug reactions in South Africa.

¹ Medicines and Related Substances Act of 1964, as amended.

² EU directive 2001/20/EC, Good Clinical practice Article 2 subsection d. & SA Clinical Trials Guidelines (2000) pg 73. See also definition by Department of Health (2004) *Ethics in Health Research: Principles, Structures and Processes*.

Good clinical practice

All trials conducted on human subjects must adhere to the official guidelines on Good Clinical Practice (GCP) as laid down in South Africa and provisions on GCP established by the International Conference on Harmonisation (ICH). ICH has expert working groups developing international ethical and scientific quality standards, amongst other things, for the design, conduct, recording and reporting of clinical trials that involve the participation of human subjects. Compliance with these standards provides assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. Researchers who care for patients in clinical trials are required to be trained in GCP, and can only participate with the approval of the MCC.

Care of patients during a trial

Research has shown that individual patients fare better, in terms of healthcare, while participating in clinical trials.³ This benefit exceeds the benefits intrinsic to any of the treatments given. Evidence shows that this effect is mediated by adherence to protocols inherent in trials. This trial effect provides overall assurance that trials are not harmful at the population level.

It is imperative that there is no third party interference with the design or implementation of the trial, i.e. with treatment to be provided to participants in the trial, irrespective of the specific type of trial (e.g. a comparison with placebo or with another registered product). Such interference may change trial outcomes and may lead to unscientific outcomes, which could place the validity of results in jeopardy. For this reason, the following principles are key tenets in clinical trials:

- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified medical practitioner or, when appropriate, a qualified dentist.⁴
- Comparators used and care given to participants in a trial have to be the same as would be given to patients ordinarily and must not drop below best proven care.⁵
- Protection of patient confidentiality and privacy must be assured. The sponsors of clinical trials do not know the identity of the participants in their trials, as this prevents bias and ensures the integrity and reliability of the outcome of the trial. It is left to the patients, individually, to decide whether to disclose their participation in a clinical trial to any third party.⁶ Where a third party discloses this information, specific, written consent from the participant, is required, and may not jeopardise the scientific merit of the trial.
- Information generated by the trial is confidential. Disclosure, to others than authorized individuals, of a sponsor's proprietary information is prohibited at all times. Investigators are required to maintain confidentiality of information provided by the sponsor.⁷ Investigators and clinical trial organizations are under contractual obligations not to disclose any information relating to the trial, including healthcare and financial aspects, to third parties.

Safety monitoring (risk to patient health)

³ Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". Braunholtz *et. al*/ Journal of Clinical Epidemiology 54 (2001) 217–224.

⁴ ICH-GCP section 2.7.

⁵ Department of Health (2004) *Ethics in Health Research: Principles, Structures and Processes*.

⁶ Report cards and related documentation are coded and the sponsors of clinical trials do not know the identity of participants in a trial. Most phase 3 trials are further "blinded" so that the patient, the care givers and the physician do not know the nature of the treatment a patient is on (or what "arm" of the study they have been entered into).

⁷ ICH-GCP section 1.6. Also refer Promotion of Access to Information Act of 2000, lawful grounds to refuse access to information.

The safety information relating to participants in a clinical trial is continuously recorded and updated throughout the conduct-phase of the trial. Patients are asked to report any untoward effects – whether they are minor or serious, they are questioned at each trial visit about possible adverse events. Researcher’s notes are also monitored and reviewed for adverse events.

Serious adverse events are defined as those that cause death, lead to hospitalisation or prolonged hospitalisation, are life threatening, lead to disability, lead to a congenital abnormality or are of a similar magnitude to the preceding definitions. Records of serious adverse events are collected and reported irrespective of the patients’ or caring medical practitioners’ opinion on the investigational products causal relationship with the event. The adverse event rate for the investigational treatment is always assumed to be the same or lower than the older therapy, should the safety monitoring process identify an excess adverse event rate this assumption may be incorrect and the trial may be stopped.

For conditions or medications where patient safety may be at particular risk a Data Safety Monitoring Board (DSMB) may be established. This board consists of doctors, ethicists, statisticians, and other health professionals that are independent of the trial and of the trial sponsor. The DSMB is mandated with the ongoing monitoring of the safety of trial participants and is given access to safety and efficacy data. This allows the DSMB to evaluate the risk benefit relationship of the investigational therapy while the trial is still running. A DSMB may ask for the trial to be stopped for a number of reasons; increased risk to patient health related to the investigational therapy, inability to prove superiority of the investigational therapy if this was postulated or because the investigational therapy works so well that it would be ethically unacceptable to continue giving patients the older therapy or a placebo.

Financial aspects of a clinical trial

Clinical trial design covers the financial aspects of healthcare provision relating to the trial. In terms of the ICH guidelines on GCP, the sponsor’s policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirements.⁸ Sponsors take out insurance cover relating to the trial, which is a condition for registration of the trial. Financial aspects are also addressed in the informed consent explained to- and signed by all trial participants. Such consent form is one of the key aspects on which ethics approval of a trial is dependent.

In view of the fact that trial participants are often more compliant than other patients and due to the financial provisions included in the trial design, the financial risk posed to participants in clinical trials themselves or to third party funders are insignificant.

Further information

More information on clinical trials is available from the following organizations which support this statement:

Innovative Medicines SA (IMSA) – www.imsa.org.za, tel 011 8804644

Pharmaceutical Industry Association of SA (PIASA) – www.piasa.co.za, tel 011 805 5100

SA Clinical Research Association (SACRA) – www.sacra.za.net

⁸ ICH-GCP Section 5.8.