

6. CLINICAL TRIALS

This section must be read in conjunction with Sections 2 and 5 of the Guiding Principles.

A clinical trial is a study involving humans to find out if a treatment or diagnostic procedure, which is believed to benefit a patient, actually does so. A clinical trial may involve testing a drug, a surgical or other procedure, or a therapeutic or diagnostic device (Other clinical or related disciplines also conduct research, which involves ethical considerations similar to clinical trials).

In pharmaceutical trials there are established codes of good clinical research practice that define clearly what is meant by a clinical trial. This section has principal application in the context of clinical drug trials but should also apply to other interventions claiming therapeutic benefit, wherever provided or conducted.

Protocols of studies involving the administration of substances to healthy human volunteers must be submitted to and approved by ethics committees.

An ethics committee must consider all aspects of the design of the trial and be satisfied that:

- The clinical trial is directed to answering a specific question, that the hypothesis is scientifically valid and that the trial medication offers a realistic possibility of benefit over standard treatment;
- The methodology provides a rationale for the selection of appropriate participants, an appropriate method of recruitment, adequate understandable information for the purpose of obtaining participants' informed consent, a clear description of the interventions and observations to be conducted, and statistical validation of sample size and outcome.

When a research ethics committee reviews a protocol for a clinical trial it must be satisfied that the protocol conforms to the spirit of these guidelines and the international documents:

- The World Medical Association Declaration of Helsinki;
- The International Conference for Harmonisation Guideline for Good Clinical Practice (ICH Guideline for GCP);
- The Association of the British Pharmaceutical Industry (ABPI) Guidelines for Medical Experiments in healthy volunteers if the study intends involving such volunteers.
- Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa and other guidelines as may be required.¹⁷

The aims of every trial should be precisely stated and every trial should be conducted by competent researchers with suitable experience and qualifications.

The use of a placebo in a clinical trial is ethically unacceptable where the use of a therapy or intervention is available, which has been demonstrated to be effective for a particular condition (also see Placebo-Controlled Trials in Appendix C). Research ethics committees should examine the costs of each trial relative to its proposed benefits and the costs relative to the use of placebo.

A research ethics committee should examine those aspects of the budgets of clinical trials that raise ethical issues, particularly capitation fees, payments to researchers or institutions or organisations involved in the research, current and consequential institutional or organisational costs, and costs that may be incurred by participants.

The research ethics committee must be satisfied that:

- No payments in money or kind could influence the findings of the research;
- There will be proper disclosure of the above aspects to the research participants.

¹⁷ For further information refer to the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, in South Africa, 2000, Department of Health, Pretoria

An ethics committee must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants for injury suffered as a result of participation in the trial.

It is recommended that ethical acceptability of a clinical trial should include a research ethics committee's evaluation of the likelihood of implementation of study findings.

Once a research ethics committee has approved the clinical trial, the researchers must:

- Conduct the trial in accordance with the agreed protocol;
- Inform the research ethics committee if amendments to the protocol become necessary, detailing – with rationale – the changes required, and seeking approval to incorporate them in the protocol;
- Inform the research ethics committee of the occurrence, during the trial, of serious or unexpected adverse effects that are likely to affect the safety of the participants or the conduct of the trial;
- Provide a report of the progress of the trial to the research ethics committee at least annually, but more frequently if requested.

It may be unethical to continue a trial for the intended period if:

- There are or have been substantial deviations from the trial protocol;
- Side effects of an unexpected type or frequency are encountered;
- As the trial progresses, one of several treatments or procedures being compared proves to be so much better, or worse, than others that adherence to the approved protocol disadvantages some of the participants.

In a clinical trial, data should be recorded accurately in a durable and appropriately referenced form and:

- Data management should comply with relevant privacy protocols;
- Data management should include levels of access and should preclude, as far as possible, the risk of tampering with the data;
- Where data is confidential, confidentiality must be observed and researchers must not use such information for their own personal advantage or for that of a third party.

The research ethics committee should ensure procedures for the continuing review and approval of each trial and determine the frequency of review appropriate to the degree of risk to participants. Such review should occur at least once a year, after which the principal researcher will be informed of the research ethics committee's decisions. A research ethics committee should require a researcher to report promptly:

- Deviations from the protocol, so that immediate hazards to trial participants may be eliminated;
- Changes that increase the risk to participants or affect significantly the conduct of the trial;
- All adverse drug reactions that are serious or unexpected;
- New information that may affect adversely the safety of all participants of the trial.

6.1 Adverse reactions and events

In South African health workers report annually an estimated 500 suspected adverse reactions of marketed medicines to the MCC ADR (Adverse Drug Reaction) centre. This means that, on average, each doctor reports only one suspected ADR in his professional career. This is in stark contrast to the fact that in several countries up to 10% of hospital admissions are due to adverse drug reactions.

Reporting suspected adverse reactions to a competent authority is an ethical duty of health professionals, especially in instances of serious adverse reactions or unknown suspected adverse reactions.

In pre-registration clinical trials all adverse events need to be reported, as the safety of products is yet to be established.

Ethics Committees have a duty to check all research protocols for suitable procedures for reporting adverse events.

- **Ethics of providing (access to) participant data**

While reporting suspected adverse events or reactions, care should be taken to ensure privacy of participants' data. Health professionals should have permission from participants to report such data. However, health professionals have an ethical obligation to report serious adverse events in the interest of future patients. Health professionals should be allowed and even obliged to provide such data, even if the participant withholds permission. ADR committees should ensure that data is anonymised when reported to others.

- **Ethics of risk or benefit decisions**

Health professionals have a duty to fairly assess risks and benefits before and while treating patients. If they are not sure of reaching a risk or benefit decision, they should consult colleagues or relevant literature.

Professionals in ADR committees who receive reports of possible adverse reactions, should fairly assess the causality of the event. Where uncertainty exists, or if the event is of a serious nature, further information should be requested.

- **Ethics of the communication of risk**

Participants have a right to know about benefits and risks of treatments, including the possibility of adverse effects. Health workers have an ethical duty to present fairly both positive and negative aspects of treatments. Participants should receive written information about such risks, either as part of informed-consent documents or as information leaflets specifically designed to inform participants.