The Evolution of Good Clinical Practice (GCP)

Prof K. Moodley, Centre for Medical Ethics & Law – University of Stellenbosch, South Africa

Dr. Lesley Henley- University of Cape Town, South Africa

Recent Research Challenges

In spite of the Nuremberg Code’s existence since 1947, American researchers regarded it as a document for Nazi doctors and scientists only. The lesson of Nuremberg seemed to have “made little impression on the American world of medical research” (Jonsen, 1998). In 1964, as a result of the Declaration of Helsinki, review of research procedures was emphasized. However, in the 1970s fraud in research was still continuing in the United States in spite of Helsinki. In the 1970s and early 1980s, the Food and Drug Administration (FDA) developed regulations on informed consent, Institutional Review Board (IRB) or Ethics Committee review and approval, and investigational new drugs.

Collectively, these regulations, along with various guidelines, became known as Good Clinical Practices or GCPs.

Japan and Europe

The first GCP guideline was issued in Japan in 1990 and in Europe in 1991. These guidelines were much less extensive and stringent than the FDA requirements. In Europe and Japan, however, these were just guidelines rather than law. And they were not widely accepted. The various GCPs were widely variable and often inconsistent. This inconsistency, together with the globalisation of many pharmaceutical companies, gave rise to the need for development of an international standard, and so the ICH process was born.

ICH GCP

Since 1991, the European Union, the United States and Japan have been collaborating in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

In 1996, the ICH Harmonised Tripartite guideline for Good Clinical Practice was released. The guideline came into effect in the European Union, the US and Japan in 1997. The ICH GCP guidelines are based on the Declaration of Helsinki (International Conference on Harmonisation, 1997). This guideline is widely used in South Africa and abroad in clinical
trial research. It forms the basis of many Good Clinical Practice training programs locally and internationally.

Although the ICH GCP guideline is not a formal international treaty or convention and is not legally binding on signatory states, its main aim is to ensure that the well-being and interests of human subjects are safeguarded. To this end, it serves as a form of quality control which maintains the integrity of data collected during trials in all countries, including those that are less well-resourced (Kaur and Choy, 2013). Its stringent quality standards allow large pharmaceutical companies to undertake increasingly more trials, at lower cost and more quickly, in developing countries. The ICH GCP guideline includes chapters on the specific roles and responsibilities of each group involved in the design, conduct and control of clinical trials: institutional review boards (IRBs)/independent ethics committees (IECs), investigators, sponsors, monitors and auditors. Thirteen principles guide the actions of these groups.

**Principles of GCP**

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the *Declaration of Helsinki*, and that are consistent with good clinical practice and the applicable regulatory requirement(s)
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society
- The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol
- A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval/ favourable opinion
- The medical care given to and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)
- Freely given informed consent should be obtained from every subject prior to clinical trial participation
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
• The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
• Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
• Systems with procedures that ensure the quality of every aspect of the trial should be implemented.

Common Criticisms of the ICH GCP guideline

The ICH GCP guideline has been criticised for catering to ‘the needs of industry and drug registration with minimal representation from academia and non-commercial organisations’ (Lang et al, 2010). The recent establishment of an online, open access forum is geared to address this gap by promoting collaboration between clinical research networks in developing countries: www.globalhealthtrials.org

A further criticism of the ICH GCP guideline is its undue emphasis on administrative and procedural duties such as stringent record keeping and standardisation of documentation, with far less attention to substantive ethical guidance, which requires researchers’ discretion, judgement and interpretation of competing ethical demands (Kaur and Choy, 2013).

On this view, the ICH GCP guideline should offer research ethics committee members and investigators a far more effective framework for ethical review and conduct of research. Thus, the ICH GCP guideline should be more specific about ‘what rights a subject has and whether they are absolute or relative, what levels of safety a subject should be provided with and what is meant by the well-being of a subject’ p. 5 (Kaur and Choy, 2013). Similarly, the guideline offers no detailed direction on how to protect ‘vulnerable’ human subjects which require ‘special attention’. ‘The ICH GCP guideline simply fails to provide IRBs with a clear idea of what they need to achieve in order to protect human subjects in general and vulnerable subjects in particular’ p. 6 (Kaur and Choy, 2013). In comparison, CIOMS guideline #13 and its commentary gives a helpful account of what it means to be a vulnerable participant, loosely defined as an individual’s relative or absolute inability to protect his or her own interests.

The 13 principles outlined in the ICH GCP guideline endeavour to offer investigators and research ethics committee members a framework to evaluate whether a proposed study is ethical. However, only 4 of the principles are directly concerned with protecting human subjects’ well-being, with the remaining principles focused primarily on the scientific merit of a study.

In addition to the ICH GCP guideline, clinical research undertaken in South Africa must comply with GCP guidelines specifically geared to the local context.
SA GCP

In 1998 the Department of Health in South Africa constituted a working group to develop guidelines for the conduct of research in South Africa. In 2000, the first edition of the guidelines for good practice in the conduct of Clinical Trials in SA was published. The document provides guidance on minimum standards that are acceptable for conducting clinical trials in SA. This guideline was updated in 2006.

The guideline covers the following areas:

- Protection of study participants
- Responsibilities of the principal investigator and participating investigators
- Responsibilities of the sponsor
- Quality Assurance
- Data management and statistics
- Multi-centred Studies
- Research Ethics Committees

Improvements in SA GCP guidance on compensation owed to human subjects injured in clinical trials have recently been recommended (Slack C., 2012).

**NB: When international guidelines clash with local guidelines or vice versa, the stricter of the 2 sets of guidelines must be followed.**

**References**

