Good clinical practice

Malik Goonewardene
Professor and Head, Department of Obstetrics & Gynaecology, Faculty of Medicine, University of Ruhuna, Galle.

Good clinical practice (GCP) does not refer to the clinical management of patients. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects [1]. Compliance with GCP ensures that the rights, safety and well-being of trial subjects are protected and consistent with ethical principles and that the clinical trial data are credible. The ethical principles applicable to research involving human subjects are found in the declaration of Helsinki of 1964 [2], which was adopted by the World Medical Association and subsequently amended several times [3], and in the International Ethical Guidelines for Biomedical Research Involving Human Subjects [4]. A guideline for GCP was developed in 1996 and adopted initially by the European Union, Japan and USA [1]. Today it is almost universally accepted. However the implementation of these guidelines varies considerably between countries. There is increasing concern that these differences in the implementation, and at times the non implementation of these guidelines may be due to a lack of knowledge or understanding of the principles of GCP.

The Clinical Trials Centre of the University of Hong Kong is currently conducting a world wide survey of GCP knowledge among clinical researchers, and they hope to develop a web based GCP training programme in the near future [5].

Principles of GCP [1]

a) Clinical trials should be conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments, the GCP guidelines, and any locally applicable regulatory requirements.

b) A trial should be initiated and continued only if the anticipated benefits justify the risks.

c) The rights, safety and well-being of the trial subjects, are more important than the interests of science and society.

d) The available information on an investigational product should be adequate to support the proposed trial.

e) A Clinical trial should be scientifically sound, and described in a clear detailed protocol.

f) A trial should be conducted in compliance with the protocol which has received prior approval by an Independent Ethics Committee.

g) Medical decisions and care should always be the responsibility of a qualified physician or dentist.

h) Each individual involved in conducting a trial should be qualified by education, training and experience to perform his/ her respective tasks.

i) Freely given informed consent should be obtained from every subject prior to his / her participation.

j) All information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

k) Confidentiality of records should be ensured to protect the identity and the privacy of trial subjects.

l) The investigational products should be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP) [6], and used according to the approved protocol.

m) There should be quality assurance of every aspect of the trial

Protocol

A clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator/s and sponsor/s. Any changes subsequently required must be similarly agreed upon and signed by the investigator/s and sponsor/s and appended to the protocol as amendments.

The protocol should be comprehensive and include the following:

Complete information regarding sponsor/s and investigator/s, literature review, rationale, justification and objectives of the study, design and method in detail, safety, quality control and quality assurance issues, data handling and record keeping, statistical analyses and ethical issues.

The GCP guidelines should be followed when submitting a research project proposal to any international organization (e.g. WHO) for consideration of support [7].

Ethical Review

Ethical issues are included in the principles of GCP. However certain aspects need further emphasis. All proposals of research that involve human subjects, and any subsequent amendments to these proposals, must be submitted for independent, prospective ethical review. Scientifically unsound research is unethical. Scientific review should usually precede ethical review. However both review committees; Scientific / Research Committee and Ethics Committee (EC), are responsible for ensuring that the research is scientifically sound [8].

Obtaining informed written consent has two components; an information statement and a certificate of consent based on it. The information statement should have a detailed description of the proposed research including purpose, procedure, risks and discomforts, benefits (to the subjects and the society) compensation payable if any, additional options for unexpected problems, right to withdraw from trial without prejudice, confidentiality and contact information for an emergency.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects [4] is a comprehensive document containing 21 guidelines. In addition to the issues considered under the GCP principles, some of the important areas covered by these guidelines include:

Research involving vulnerable persons e.g. children, adolescents, women, mentally retarded or unconscious patients.

The use of controls and placebos.

Rights of injured subjects to treatment and compensation.

Obligations to provide health care services.

The following should be submitted to the EC for approval before commencing a clinical trial:

Qualifications and curriculum vitae of investigators.

Trial protocols and amendments.

Subject recruitment procedure.

e.g. advertisements.

Written information provided to subjects.

Written informed consent form.

Clinical and non clinical data including safety information of the investigational product/s.

Information about payments and compensation available to subjects.

The EC should review ongoing clinical trials at least once per year.

Monitoring

All trials involving human subjects should be monitored right through from its commencement up to the final report. This is to ensure that:

The rights and well being of the subjects are protected.

The trial is being conducted in accordance with the approved protocol and any subsequent amendments too have been approved.

The principles of GCP and any other local requirements are adhered to

The trial data which would be reported are accurate, complete and verifiable from source documents.

The trial data are credible

Research, Audit and Evidence Based Medicine

Many clinicians often confuse clinical research with audit. Clinical research will answer the question "What is the best / correct thing which should be done?" Clinical audit will answer the question "Is the best / correct thing being done?" Clinical audit involves the systematic and critical analysis of various aspects:

a) Quality of Care: Diagnosis, Treatment, Care.

b) Use of resources

c) Outcomes (cure / disability)

d) Quality of life

Both clinical research & audit are thus interlinked and involved in the practice of Evidence Based Medicine (EBM). The practice of EBM involves

the critical appraisal of best external evidence which is usually obtained by research, and its integration with clinical expertise (clinical judgment, skills and experience), taking into account the facilities available and the individual characteristics and preferences of the patient. After adopting EBM, clinical practice should be subjected to audit and feed back to further improve it [9].

Integrity

Integrity is essential in any sphere of life and research is no exception. Striving towards peer recognition and advancement in academic career and position can challenge a person's integrity. A study carried out in Germany in 1998 found that 24% of 347 research publications examined had either definitely or highly probably been manipulated [10]. In the UK there is a Committee on Publication Ethics which deals with suspected research misconduct. It has been recommended that academic centres should educate their researchers, and also have self assessments and external peer review, to promote integrity in research [10]. "Rather fail with honour than succeed with fraud"- Sophocles.

Conclusion

All research involving human subjects should be scientifically sound, conform to ethical principles and have credible data. All those who are involved in clinical research must have a comprehensive knowledge and understanding of GCP and GCP related issues.

References

1. ICH Expert Working Group. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. ICH Guidelines for Good Clinical Practice 1996; 1.
2. World Medical Association. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly. Helsinki, Finland. World Medical Association 1964.
3. Word Health Organization. Declaration of Helsinki in: Preparing a research project proposal: guidelines and forms (4th Ed) WHO Special Programme of Research, Development and Research Training in Human Reproduction. WHO / HRP/ PP/ 2003; 17-21.
4. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Council for International Organizations of Medical Sciences. Geneva 2002.
5. Carlberg J. Clinical Trails Centre The University of Hong Kong. www.hku.hk/h9805196.
6. World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations. Good Manufacturing Practices for Pharmaceutical Products. Report 32. WHO Technical Report Series No. 823. WHO Geneva 1992.
7. Word Health Organization. Preparing a research project proposal: guidelines and forms (4th Ed) WHO Special Programme of Research, Development and Research Training in Human Reproduction. WHO / HRP/ PP/ 2003; 2-12.
8. Word Health Organization. Guidelines for the establishment of Scientific and Ethical Review Bodies in: Preparing a research project proposal: guidelines and forms (4th Ed) WHO Special Programme of Research, Development and Research Training in Human Reproduction. WHO/ HRP/ PP/ 2003; 52.
9. Sackett DL, Richardson WS, Rosenburg WA, Haynes RB. Evidence Based Medicine: How to teach and practice EBM. London: Churchill Livingstone, 1998: 1-19.
10. Editorial. The Next Step: Ensuring Integrity of Scientific Research. *The Lancet* 2002; **360**: 499.