EDITORIAL

Good Clinical Practice: Issues and Challenges

M I Merican, FRCP, Deputy Director General of Health (Research and Technical Support), Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials involving the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, integrity and confidentiality and well being of trial subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki and that the data and reported results are credible and accurate[1].

Clinical trials should be based on good science, are well designed, properly analyzed and conducted in accordance with GCP. Failure to do so may either put trial subjects at risk or result in the rejection of clinical trial data submitted by health authorities and the scientific committee. Needless to say the credibility of the researcher and the research institution he works in may be questioned. The Ministry of Health of Malaysia (MOH) is therefore making it mandatory for all investigators involved in clinical trials to have approved GCP training and certification. The Malaysian Guidelines to GCP has been launched to help investigators and pharmaceutical or related healthcare companies to be familiar with the procedural and regulatory requirements of GCP in Malaysia.

GCP was born in the USA in the mid 1970s when the Food and Drug Administration (FDA) implemented guidelines for clinical investigators. Subsequently rigorous investigational new drug (IND) procedures were enforced and regularly updated over the years to the version that is in force today. Because of the strict implementation of the new regulations in the USA, the FDA found it necessary to reject data from other countries which it considered to be of substandard quality. This development left the other countries with little choice but to review their own procedures resulting in the birth of various national GCPs. Eventually, a set of European GCP Guidelines was developed and implemented in 1990. Japan, the third largest pharmaceutical market developed their own GCP Guidelines in 1991.

Unfortunately the development of the various GCPs did not solve the problem of acceptability of data as there were, not surprisingly, differences in GCP procedures in Europe, USA and Japan. So data collected in one region would not be automatically accepted by another regions despite the data being generated from studies conducted in accordance with local GCP requirements.

A series of meetings held between the regulatory authorities and representatives of the pharmaceutical industry companies in the USA, Europe and Japan, together with observers from Scandinavia, Australia, Canada and the WHO (collectively known as ICH) gave birth to a set of GCP guidelines that would be universally accepted. In May 1996, the ICH GCPs came into being and is now the standard by which all clinical trials have to be performed in order to achieve universal recognition. In 1997, the European Union accepted the ICH GCP as a legal requirement and since May 1997, the FDA expects all trials conducted outside the USA, especially those used to support applications for marketing authorization (NDA, new drug application) to be conducted in accordance with the ICH GCP Guidelines. Japan implemented the ICH GCP Guidelines in April 1997.

In Malaysia, clinical trials conducted before 1996 were usually uncontrolled Phase IV or post-marketing studies. There were only a handful of late Phase IV

clinical trials. With the greater emphasis on the evidence-based approach in clinical practice based on quality research, the greater commitment by the MOH in facilitating clinical research coupled with the resurgent interest shown by clinicians in clinical research, there has been a significant increase in the conduct of clinical trials in Malaysia, especially over the last 2 years. In 1996 there were only 2 Phase III and 8 Phase IV clinical trials whilst in 1999, there were 2 Phase I, 5 Phase II, 21 Phase III and 8 Phase IV trials.

The principles of GCP recommended by the ICH Harmonized Tripartite Guidelines for GCP focus on the rights and protection of human subjects, the trial itself, the Protocol, the roles, responsibilities, qualifications and experience of the investigators, the procedures involved and the investigational products under study[2].

To protect the rights of subjects, all clinical trials should be conducted in accordance with the ethical principles based on the Declaration of Helsinki and are consistent with the applicable regulatory requirements. The clinical trials taken should also weigh foreseeable risks and inconveniences against the anticipated benefits 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 interests of science and society and any trial taken must include freely-given consent to take part in a clinical study. In addition, trial subjects can withdraw from studies at any time without giving a reason and such withdrawal does not prejudice any future medical treatment.

Freely given informed consent should be obtained from every subject prior to clinical trial participation. Written informed consent should be obtained from each patient in accordance with regulatory requirements and the Declaration of Helsinki. Both the person taking the consent and the patients should personally sign and date the consent form in the presence of a witness present during the whole consent procedure. The witness too will be required to sign.

The language used must be simple enough for the trial subjects to fully understand the purpose of the study and how it affects them. The responsibilities of the sponsor, the investigators and their own responsibilities have to be made known to them. The subject should be given this information both verbally and in writing and an information sheet should be provided for each subject.

The subjects must also be made aware of any compensation in the event of injury or death and that the sponsor provides indemnity insurance to cover the liability of the investigator and the sponsor in the event of any untoward event that may occur in subjects taking part in the study.

The confidentiality of records that could identify subjects must be maintained, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

The proposed clinical trial should be supported by adequate non-clinical and clinical information on the investigational product under study. It should also be scientifically sound and described in a clear detailed protocol.

The protocol is the formal record of how the trials must be conducted and must be clear and detailed. The protocol must have the prior approval of the Institutional Research Review Committee and its Ethics Committee. No modification should be made without prior consultation with the sponsor, unless it poses immediate danger to subjects under the study. All agreed protocol amendments must be documented and approved by the Ethics Committee prior to implementation, unless they are purely administrative in nature.

The composition of the Ethics Committee must fulfill the ICH-GCP requirements. The Ethics Committee should safeguard the rights, safety and well-being of all trial subjects.

Throughout the trial, 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. All investigators involved in the trial should be qualified by education, training and experience to perform his/her respective tasks.

The investigator must have the time and the discipline to do the study. He or she must also provide the sponsors with an up-to date, signed and dated CV as evidence of his or her qualifications. In addition, he or she must provide evidence of suitable post-graduate experience in the specialty under study, backed by relevant publications if possible. He or she must be fully aware of the proper use of the investigational product, be thoroughly familiar with the study protocol and be at all times compliant with his or her GCP responsibilities. A common problem is the inability to meet study recruitment targets and this issue needs to be given special consideration.

All trial procedures should be consistent with GCP/applicable regulatory requirements. All clinical trial information should be recorded, handled and stored in a way that allows for accurate reporting, interpretation and verification. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

The case report form (CRF) is usually prepared by the sponsor of the study. The investigator should ensure that the pages in the CRF are completed, fully and legibly, at every visit and that all data recorded in the CRF must be properly done to allow verification during the process of source data verification. There are strict rules for amending data in CRFs. Recording of data, done in accordance with GCP requirements, can be very tedious but necessary to ensure integrity of data. The investigator must co-operate fully with the study monitor in this somewhat demanding exercise. ICH GCP requires the study monitor to have direct access to all subject files to ensure that all data that have been recorded is correct. An important part of GCP is the collection and maintenance of documents in the trial that demonstrate adherence to all the GCP requirements.

All adverse events must be properly recorded. The investigator must obtain information from the subjects about any adverse events that may have occurred as this information may not be readily offered by the subject, unless specifically asked for. An adverse event is any untoward medical occurrence in a trial subject who has been administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment. All adverse events must therefore be recorded. Serious adverse events, as defined by study protocol, must be reported immediately to the sponsor. The Ethics committee must also be informed of serious, unexpected adverse events that are product-related.

Investigational products should be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP) and used in accordance with the approved protocol.

In the past, most clinical studies in MOH hospitals were conducted rather diffidently by clinicians, at the behest of pharmaceutical companies. Many did not anticipate the amount of time and commitment required to ensure the successful completion of a research project. While some abandoned trials they had initiated out of sheer desperation, despair and frustration, others infuse themselves with greater commitment and renewed vigour and enthusiasm for the successful completion of the studies. The ignorance and lack of understanding of the discipline and commitment involved in the conduct of clinical trials were fairly widespread amongst clinicians some years ago.

Many problems related to the conduct of clinical trials have surfaced over the years. These include the lack of commitment of busy clinicians whose clinical responsibilities and training and travel commitments leave little time for proper clinical research. Many cannot commit to monitoring visits and in fact view such visits with much disdain. Others delegate their duties to uninitiated and misinformed subordinates or go on sabbatical leave, leaving the project in jeopardy. The lack of co-ordination between the investigators and the clinical research assistants are also common.

Many investigators over-estimated their capability to recruit trials subjects resulting in slow study recruitment, which inevitably affects budget, timelines and delayed publications. It has been reported that in USA for each day's delay in getting Food and Drug Administration (FDA) approval of a drug, the manufacturer loses, on average, USD 1.3 billion. To ensure speed in completion of clinical trials, there is a growing move on the part of sponsors to employ contract-research organisations (CROs) to oversee drug-

related clinical trials[3]. Protocols are often not adhered to and many new investigators find faults with protocols they had agreed to, prior to the commencement of the study. There is also poor maintenance of drug dispensing and drug logs. Other deviations from GCP include protocol violations, illegible and incorrect records, missing data, misplaced case report forms (CRFs), problems in informed consent, over delegation of the research assistant or study co-ordinator and lack of training of investigators. Test results required by the protocol are sometimes either not done or not available on time. Many clinicians when informed of these deviations get infuriated, not at themselves, but at the auditor who brings these to their attention.

The responsibilities of the sponsor, the monitor and the investigator must be fully understood by all parties involved in the study. The cost of individual clinical trials has escalated substantially since the implementation of GCP. Clinicians who undertake clinical trials must be fully aware of the importance of conducting the study efficiently and in the shortest time possible.

For successful implementation of the study, the investigator will need a good team including a good research assistant and efficient and committed co-investigators who are familiar with GCP and the study protocol. Enough time must be devoted for the study with regular meetings being held to discuss progress and problems pertaining to the study. Proper and accurate documentation is crucial and cannot be compromised at any cost.

The setting up of the Network of Clinical Research Centres (CRC) under the National Institutes of Health by the Ministry of Health in the Seventh Malaysia Plan (7MP, 1996 - 2000) and the formation in 1997 of a national committee on clinical research, comprising MOH officials, researchers, pharmacists, pharmacologists, clinicians from MOH and local universities, members of regulatory authorities and representatives from the pharmaceutical industry have all boosted the interest, importance and quality of clinical research in this country. The production of the Malaysian Guidelines for GCP, the Guidelines for the application to conduct drug-related clinical trials in Malaysia and guidelines for clinical trial import license have facilitated the application and conduct of clinical trials. Training in GCP have intensified throughout the country and to date, approximately 100 clinicians have been provided formal training in GCP. Clinical research has also been identified as one of the priority areas for research under the eight Malaysian Plan (8 MP, 2001 - 2005). The scene has therefore been set and the infrastructure made available to enhance the research capacity and capability of our clinicians to conduct quality clinical research, in accordance to accepted world standards.

The MOH will soon be producing a directory of trained, experienced, competent and capable researchers from amongst the clinicians who are ready to take up bigger and more ambitious challenges in the field of clinical research. Such an exercise will take into consideration the area of interest, specialization and expertise of the clinicians. The availability of such a directory will naturally result in more competitive bidding for clinical research projects and hopefully this will generate healthy competition amongst clinicians, not only in this country, but also in this region. Many countries in the Asia Pacific Region have decided to emulate this initiative proposed by Malaysia at a recent APEC Coordinating Center for Good Clinical Practice meeting in Singapore. The challenge is for clinicians in participating countries to be outstanding in their area of expertise in order to attract the best studies from the best pharmaceutical companies and other interested international research organizations.

Clinical research in Malaysia needs to be coordinated and not duplicated, hence the need for greater collaboration amongst researchers in the various research institutions. Clinical research conducted in MOH hospitals will conform to this format with the setting up of the CRC. Discipline -oriented clinical research will of course be the best way to ensure good quality research, provided all experts in an area of clinical interest co-ordinate their research activities and are willing to share information regarding the type and progress of research projects they are undertaking. This exchange and amalgamation of research ideas will also allow for priority setting and chart directions and thrusts in particular areas of clinical research, in consonance with the national needs. In a sense this may be a form of top-down research and not entirely researcher -driven, which may fall prey to the narrow interest of the wayward researcher.

To remain or be competitive, we have to achieve and adhere to international standards. Efforts to attain international recognition should not stop at compliance and adherence to GCP. Our laboratories, especially those in the major research institutions will have to achieve Good Laboratory Practice (GLP) status and current ISO standards. Although this is going to be a more demanding and difficult exercise, it is not an impossible task. We are now conducting a nationwide survey of all the major laboratories and research centres to appraise the available infrastructure and human resource and identify strengths and weaknesses in terms of their capacity and capability in embarking on more ambitious and varied forms of clinical research.

Such efforts are necessary to galvanize efforts to embark on drug discovery and development and undertake more ambitious Phase I, II and III studies. There is great potential for instance in the development of herbal medicinal products in this country.

Facilities for Bioequivalence (BE) studies have to be expanded and studies focusing on drug-drug interactions and drug-related morbidity and mortality have to be promoted to ensure the efficacy, safety and quality of drugs used in Malaysia, especially with the current tide of using generic drugs preferentially in MOH hospitals because of much lower costs. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects can be expected to be essentially the same. In countries such as Canada, USA, UK, EU, Japan, Australia and Germany, BE studies are mandatory for generic products (in solid oral dosage forms) registration. In Malaysia, efforts are being made to encourage the industry to perform BE studies and the MOH will assist them in this endeavour.

From the year 2000 onwards, no clinicians without approved GCP training should be appointed as principal investigators in clinical trials. The reasons for this are clear enough and do not warrant debate. Without GCP, subjects participating in clinical trials may be at risk, the data collected may be unreliable and the results of the study may be rejected outright by all stakeholders in health.

The launching of the Malaysian Guidelines for GCP and the many workshops on GCP bears testimony to the commitment of the MOH to ensure excellence and quality of clinical research conducted in this country. With more co-ordinated research efforts with the universities and established research institutions, designated centres of excellence in specific clinical areas relevant to this region may soon be a reality. A lot remains to be done in our efforts to achieve excellence and mastery in the conduct of clinical research in this region.

References

1. Hutchinson D. The Trial Investigator's GCP Handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd. 1997.
2. ICH Harmonised Tripartite Guideline for Good Clinical Practice (2nd ed). Brookwood Medical Publications Ltd., 1997.
3. Bodenheimer T. Uneasy Alliance-Clinical Investigators and the Pharmaceutical Industry. N Engl J M 2000; 342: 1539-44.