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Good clinical practice and the clinical pharmacologist

What is good clinical practice?

Good clinical practice (GCP) is the name applied to a series of guidelines which specify points required for clinical trials to be acceptable to regulatory authorities. As might be expected, different bodies have produced separate GCP guidelines and whilst they are broadly similar in the points they cover, details vary between the different bodies. This article will concentrate on the general principles of GCP and point out some differences which exist between different regulations.

The purpose of GCP is to ensure good quality data suitable for assessment by the regulatory authority. It also aims to avoid any possibility of fraud either by the company or the investigator. Clearly these are laudable aims but to achieve them the amount of paperwork required of the company and investigator has multiplied considerably. The net result of the application of GCP to clinical trials is likely to be a reduction in the number of trials but, hopefully, some improvement in their quality.

GCP guidelines are just that – a set of guidelines rather than rules. Only in the Irish Republic do the provisions have the force of law, the Dail having enacted some of the GCP provisions in the Control of Clinical Trials Act. The introduction to the American GCP guidelines confirms that they are a set of principles and not legal requirements – they represent a standard of practice which is acceptable to the FDA. It is clear, however, that a company which adopts different procedures for monitoring clinical investigation will have to submit them to the regulatory authorities for review and comment. Adherence to the GCP code of practice may avoid rejection of a submission on the grounds of inadequate procedures. Because the guidelines from various regulating authorities, e.g. the FDA, EC, Nordik, are slightly different, individual pharmaceutical companies and contract research organisations have drawn up their own guidelines which attempt to embrace all those currently recommended. These guidelines are known as standard operating procedures or SOPs.

Jargon is common in both GCPs and SOPs, and the following terms are frequently used. A *sponsor* is the organisation (usually the pharmaceutical company) which is responsible for the initiation, management and financing of the clinical trial. The sponsor liaises with the *investigator* via a designated and suitably qualified employee known as the *monitor*. *Quality assurance* is the term given to a planned series of actions necessary to provide confidence to the regulatory authority that the data generated will satisfy its requirements. *Quality control* refers to procedures used to monitor trial conduct and detect and eliminate unsatisfactory performance. *Verification* is a term used for systematic examination of the trial data during and after the trial by the sponsor or the regulatory authorities.

The players

Under the GCP guidelines each of the nominated individuals, the investigator, the monitor and the sponsor, has a series of clearly defined roles. The sponsor must select the investigator, and ensure that he is appropriately qualified, has sufficient experience, and has time to devote to the study. The sponsor must also ensure that the study can take place in the location designated. Support staff must be adequate and the APBI guidelines specifically suggest that the personal availability of the investigator should be explored. If the investigator appears to be disorganised and rushed, 'questions ought to be raised about scheduling, staff and his management of time. It is safe to anticipate that over-extended or disorganised clinicians will have little time to fill out case report forms, to keep records, to return telephone calls or to discuss the study.' It may be difficult to find clinicians who are not over-extended! The sponsor has also to ensure that an adequate patient population is available for the investigator to complete the study within a realistic time. The sponsor is responsible for drawing up the protocol of the study, which must be designed so that it is sufficiently sensitive to measure the putative effects of the drug under investigation. Most GCPs include a checklist of requirements for a standard protocol including a clear statement of study objectives, rationale, design, drug treatment plan, parameters to be assessed, and details of follow-up and adverse events. Close adherence to these protocol checklists probably explains the uniformity of many protocols recently.

The monitor is responsible for overseeing the progress of the study and ensuring adherence to the protocol. The monitor's duties are laid out and include pre-trial visits to all parties engaged in the conduct of the trial, pre-determination of laboratory procedures and, if necessary, random checking of reference samples during assays. The monitor is also obliged to visit the investigator during the study to check raw data and ensure correct filling out of clinical record forms.

The investigator is required to sign a formal agreement with the sponsor and to ensure that Ethics Committee approval is obtained. A copy of the Ethics Committee approval must be lodged with the sponsor. The investigator is responsible for ensuring that each patient entered into the study has properly completed a consent form, and for the collection and entry of data into the case report forms. These forms must be kept 'as long as is practicable'. Finally, the investigator is responsible for agreeing a global figure for the cost of the study at the outset of the trial.

Implications for clinical research

Implementation of GCP will inevitably increase markedly the costs of trials sponsored by the

pharmaceutical industry. The additional paperwork, quality control and verification of trial data will all inflate the cost. The investigator will need to arrange storage of all records of the trial. The length of time that records must be retained varies between guidelines. For example the EC GCP recommends that data should be retained for at least 5 years, whereas the ABPI guidelines suggest a minimum of 10 years. Investigators will clearly have to allow for prolonged storage of large volumes of data when calculating the costs of performing clinical trials in the future.

Perhaps the most contentious issue raised by GCP guidelines is the monitoring of studies by independent regulatory authorities and the sponsor. The FDA guidelines state that the most effective way to assure the accuracy of data submitted is to review individual subject records and other supporting documents, and to compare these with reports prepared by the investigator for submission to the sponsors. This may be interpreted as requesting the review of confidential clinical notes by the monitor. The APBI guidelines suggest that a random inspection of work procedures should be carried out by an external monitor appointed by the regulatory authorities. There is clearly an ethical dilemma concerning access to confidential clinical records by individuals not concerned with patient management. It appears that the regulatory authorities wish to review clinical records mainly to ensure that the patients entered into trials do actually exist. A satisfactory compromise agreed with the Ethics Committee of my own hospital is that any audit of records should be performed as a 'back to back' procedure with the investigator reading from the clinical records any details required by the investigating authority. In this way patient confidentiality may be maintained whilst ensuring the accuracy of any information required. An alternative method might be to include in the consent form a paragraph seeking the patient's consent for an independent regulatory authority to view their clinical notes.

It is clear that implementation of GCP will require close liasion between investigators, sponsors, ethics committees and regulatory bodies. Unless these procedures are handled in a sensitive manner there is a danger of provoking confrontation. GCP needs to be thought through at the outset so that the necessary bridges are in place before trials begin.

Conclusions

GCP is with us whether we like it or not. At present it applies only to trials which are to be submitted to regulatory bodies, but there may be increasing pressure from peer review journals to apply some form of GCP to any work submitted. The objective of GCP is not to enforce blanket uniformity of trials but to ensure minimum standards of scientific and ethical conduct. The design of studies will undoubtedly have to be modified to accommodate GCPs. In the various guidelines there is little that seems objectionable and much which will promote high standards of research. Implementation of GCP will entail more work for the pharmaceutical industry and clinical investigators alike. The end result should however be higher quality of clinical trials which will hopefully provide a sound basis for prescribing practice.

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A. MORICE
Department of Medicine and Pharmacology,
Royal Hallamshire Hospital,
Glossop Road, Sheffield S10 2JF

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