**Good clinical practice: a nuisance, a help or a necessity for clinical pharmacology?**

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This article reviews the impact of good clinical practice (GCP) on clinical pharmacology with particular reference to the new European Union Clinical Trial Directive. The Directive will be applied to both commercial and noncommercial studies on medicinal products for human use. The Directive requires that GCP should be used in all clinical trials except noninterventional studies. GCP is likely to follow the International Conference on Harmonization GCP guidelines in many aspects. GCP will enforce tighter guidelines on ethical aspects of a clinical study. Higher standards will be required in terms of comprehensive documentation for the clinical protocol, record keeping, training, and facilities including computers. Quality assurance and inspections will ensure that these standards are achieved. The additional requirements of GCP are discussed and any advantage to the study subject. The impact of the new Directive within the Research Governance Framework of the UK Department of Health is reviewed.

**Keywords:** clinical protocol, clinical trial directive, ethics committees, GCP, good manufacturing practice, ICH GCP, inspections, laboratories, quality assurance, research governance framework, Resuscitation Council, validated computers, volunteers

**Introduction**

There is no doubt that good clinical practice (GCP) can be seen as a nuisance. GCP demands more of the clinical researcher in time, resource and money. In return the data obtained from clinical trials conducted in accordance with GCP should be more reliable, having undergone an extensive quality control process. The required input of a qualified statistician in the design and method of analysis of the research project should promote a more satisfactory result of the study. The vigorous ethical requirements of GCP for the protection of the study subject will improve their rights, safety and well being. Whether we would wish otherwise or not, GCP has become a necessity since it is to be law (European Union (EU) Directive (2001/20/EC)) [1].

**What is good clinical practice?**

Until comparatively recently, GCP was dependent on the judgement of the clinician and to a lesser extent, their peers. As far as clinical trials were concerned, this situation was felt to be unacceptable to regulators with responsibility for approval of new drugs from the drug industry. As a result, many national and international organizations provided versions of a guideline described as good clinical practice. The Declaration of Helsinki in 1964 and subsequent updates [2] provided a basis for these versions. For the independent researcher and for the clinical trial that had a noncommercial sponsor, it was felt that GCP was too restrictive, too demanding and bureaucratic. Changing the perceived correct terminology did not help the situation. Good research practice (GRP) had been used in clinical research, particularly in academia, and GCP had appeared to have taken on suddenly those principles associated with all clinical research. The purist may argue that there are differences between GCP and GRP, but the passage of time has inflicted on them the same meaning. GCP and GRP describe a way of thinking that becomes an attitude to work when conducting research in human subjects. It is these attitudes that have now become the concern of regulators not only for commercial research but also for noncommercial research.

**EU Directive and GCP**

The question requires to be asked whether the GCP quoted in the title refers to the use of GCP in the trials
sponsored by the drug industry or the GCP used by the independent researcher associated with academia and with noncommercial studies. Whatever the arguments were for different standards of GCP to be used in commercial and noncommercial studies, GCP now refers to both types of pharmacological research involving human subjects. The new EU Directive (2001/20/EC) applies to all clinical trials on medicinal products for human use, including Phase I studies. Only so-called noninterventional trials as defined by the Directive are excluded. A noninterventional trial is one where the assignment of the patient to a particular therapeutic strategy is not decided in advance by a protocol, and no additional diagnostic or monitoring procedures are undertaken. Part of the Directive is the provision for various guidelines to be prepared by the European Commission including one on GCP. Undoubtedly, they will be based on those of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [3].

International Conference on Harmonization

In the drug industry, ICH has brought the drug regulatory authorities of the EU, Japan and the United States together with experts from the pharmaceutical industry. The clinical pharmacologist should become acquainted with the ICH publications, as many of its guides may be relevant to their work. Apart from a guideline on GCP, topics [4] as diverse as clinical studies in geriatrics and paediatric populations; statistical advice; and the ethnic factors in the acceptability of foreign data have been prepared. Recently, agreement has been achieved between the EU, Japan and the US to reduce repetitive research by describing the organization of a common technical document for the registration of drugs [4, 5]. However, does an organization formed and supported by the private drug industry to ease the passage of new commercial drugs to the global market have relevance to noncommercial research projects?

Disparagers of GCP as outlined in the ICH GCP guidelines felt that it need only be followed for potential drugs destined for the US market and by those sponsored by the drug industry. The US regulatory authorities not only had imposed their version [6, 7] of GCP on the clinical trials but also carried out inspections to confirm that documentation relating to GCP was available and correct. The documentation and the rigorous monitoring required by GCP were perceived to create unnecessary bureaucracy and increased administration, leading to delays in vital clinical research and increased costs. If this were true, with the advent of the new EU Directive, noncommercial research projects would be reduced and vital medical research conducted at many European academic institutions curtailed. An alternative argument could be proposed that research undertaken with human subjects requires the same rigor both scientifically and ethically whether undertaken in noncommercial or commercial environment. Some would suggest that poor monitoring of data, inadequate statistical design and analysis, and dubious consent and ethical approval procedures have weakened the viability of data in noncommercial clinical research just as it frequently occurred in the past, and sometimes still does, for clinical trials driven by the drug industry.

The need for GCP

Although most of the published reports of misconduct in clinical trials [8–11] are from outside the UK, the UK Department of Health Research Governance Framework [12] notes, ‘there is growing public and professional concern about research misconduct and fraud though its extent is unknown’. A recent published paper suggests that ethical approval may not always be sought [13]. Complacency in the quality of noncommercial studies in the UK would be misplaced.

The clinical pharmacologist needs to examine whether GCP can add to the quality of their work and try to establish the most efficient and effective way to adhere to its principles. Many clinical trials involve too many demands on the study subject and collect too many data in attempt to answer too many questions. Well-planned simpler trials may provide the key answers to the questions being asked. Much of the practical emphasis of the ICH GCP is on providing documentary evidence that independent ethics committee (IEC) approval and informed consent has taken place, a comprehensive protocol has been followed, and source documents such as medical records confirm that a subject has participated in the study. In addition, any substance or device used in a clinical trial has to meet certain specific standards such as pharmaceutical standards of purity for a study drug and the use of validated computer systems. To most observers, these are not unreasonable requirements.

Ethical aspects of GCP

Ethical questions of clinical research should never be underestimated. The ethical principles of the Declaration of Helsinki have had a profound influence on GCP and the accepted way that clinical research is undertaken. Clearly, there is an ethical question as to whether the foreseeable risks and inconveniences to the study subject in participating in the research project are outweighed by the anticipated benefits to that patient. Even more critical
is the question whether the risks being undertaken by the healthy volunteer are considered acceptable when the volunteer will not benefit medically from the study. Most people recognize the need for better medical treatments. However, there are many examples in modern history where the risks to the individual trial subject have outweighed any benefit to either the subject or society. Society is rightly wary of medical research involving human study subjects.

GCP requires that before a clinical trial begins an independent review should take place of the proposed project. The IEC that will carry out this review will need to demonstrate its independence. It will be required to establish that the scientific approach is current, the motivation clear and the processes unambiguous, and there should be sufficient data to judge the safety and effectiveness of the interventions proposed. This cannot take place unless a suitable protocol, information sheet and consent form are prepared.

**GCP and the clinical protocol and consent form**

ICH GCP has conveniently outlined the contents of a study protocol in chapter 6 of its guideline. In the past, many protocols, whether for a clinical trial paid for by the drug industry, academia or government, have been poorly prepared. IECs have been presented with protocols that have been incomprehensible to all but the writers, with important aspects missing, such as the length of the study and the description of the statistical analysis. The protocol should encompass all aspects of a planned study in a language that can be understood.

Linked to the protocol, there should be a copy of the information sheet and consent form that will be provided to the study subject to read and sign before entering the study. The IECs must approve these documents. In the past, consent forms used by patients for routine hospital procedures have been used for clinical trials. These are not appropriate. The new EU Clinical Directive stipulates that consent should be obtained before the study starts and that information should be provided for the subject.

Specific items including the purpose of the study, the subject's responsibilities, the study procedures, foreseeable risks and benefits need to be provided in the information as described in ICH GCP (chapter 4.8). This section of the guideline covers other arrangements for consent when the subject is too ill, a child or mentally handicapped. One can ask where is the unnecessary bureaucracy in these requirements of GCP, which are designed to protect the patient or healthy volunteer participating in a clinical project?

Frequently, the independent researcher will wish to modify the protocol or consent documents after the IEC has approved them. In the past, a quick discussion with the chairperson of the IEC has usually sufficed, resulting in changes to the medical treatment or statistical analysis of the study. Frequently, these revisions should have received greater deliberations before any change is made. GCP requires a formal approval by the IEC of any changes apart from the most pedestrian and requires this approval before the new protocol is put into practice. Again, there have to be strong arguments for the changes, which tightens ethical approval of new versions of the protocol and consent form. However, because of short timelines, clinical pharmacologists may argue there is sometimes a need for expedited review of protocol amendments. Although, this might be a valid point, inspectors from the regulatory agencies would still consider it to be inappropriate for the IEC chairperson alone to provide approval for a significant protocol amendment. If the IEC establishes an expeditious review process, then this should be included in the IEC's written procedures.

**Record-keeping and GCP**

ICH GCP also requires a thorough approach to record keeping, the handling of data and the statistical analysis of results. Individuals involved in these tasks should be qualified and trained. This applies not only to the medical staff but also to those specialists such as computer staff who validate the computer systems and to the statistical specialist employed to plan and analyse the data. Adverse events are required to be monitored and reported to the IEC and to the pharmacovigilance sections of the health authorities when serious, unexpected or related to the treatment. The reporting requirements to the health authorities vary from country to country. Source documents such as ECG recordings, laboratory data, subject diary cards and subject records should be kept for audit trail purposes. The subject's medical history needs to be actively sought to avoid violations of the inclusion criteria and to protect the subject from harm. A national volunteer register could be suggested to eradicate 'professional' volunteers.

**Monitoring**

Monitors should confirm the accuracy of the data as well as protocol compliance. Most independent researchers have relied on a member of their own staff or themselves to conduct the so-called source data verification. In the past, inspectorates have found major deficiencies between source documents and the Case or Clinical Report Form. The use of independent monitors although costly, has to be encouraged to achieve adequate quality control to GCP standards. However, the independent monitor may not be required in every clin-
ica] trial for noncommercial research. This additional cost can sometimes be saved if a suitable risk analysis has been performed and documented, the research personnel are appropriately trained and a suitable quality system is in place.

**Facilities and equipment**

GCP requires that suitable facilities and appropriate study drugs be used for clinical trials. This will include laboratories that work to the principles of Good Laboratory Practice, validated computers [14], secure archives for both paper and electronic documentation, and proper resuscitation facilities meeting the requirements of such organizations as the Resuscitation Council (UK) [15]. Study drugs will need to be prepared to the principles of Good Manufacturing Practice [16] with all the accompanying documentation. The EU Directive acknowledges that some noncommercial clinical trials may rely on pharmacy preparations of study drugs rather than extensive manufacturing procedures associated with a commercial study and sponsor.

**Quality assurance and outsiders**

Another effect of GCP and the EU Directive on the clinical pharmacologist is the increased influence from independent individuals and institutions. Apart from the role of the IEC and in some cases the use of the independent monitor, external auditors and inspectors from quality assurance (QA) units and government agencies will be involved. QA auditors will be employed to review clinical trials and give advice in preparation for future government inspections. One of the main roles of the QA auditor will be to establish whether there are adequate quality control procedures in place. Government inspections will not be undertaken for all studies. The volume of work and cost prevents such an undertaking. It is anticipated in the UK that cyclical, mandatory GCP and GMP inspections (where applicable) of units involved in clinical pharmacology studies will take place when the EU Directive is implemented.

This perceived ‘policeman’ role by QA and the inspectorate could appear very intrusive. ‘Outsiders’ will review medical records and other confidential source documents. The subject’s permission will need to be obtained and documented during the consent procedure before their confidential documents are examined. To some independent researchers, these additional checks on their professionalism can be destructive. They would argue that their work is already of a high standard and does not need these additional inspections. The independent researcher could suggest an alternative approach that depends on the individual clinician and their staff self-monitoring their work. In the past, this has resulted in inadequate data from poorly designed trials leading to unsound scientific publications and additional studies. Sometimes, this has caused incorrect assumptions and possible hazards to patients. If the quality assurance process is treated in a constructive manner, much can be gained.

**Reports**

Another so-called tedious procedure required by GCP is the preparation of study or clinical reports at the end of the study, even if the clinical trial has been stopped after only one or two subjects have entered the study. On reflection, this GCP requirement makes sense because the reporting of negative results can be as useful as positive results. In addition, the clinical pharmacologist is encouraged to prepare properly before commencing a study, thus avoiding the premature stopping of the study other than for unpredicted safety issues.

**The situation in the UK**

In the UK, there appears to be a surfeit of guidance documents on how to conduct research in National Health Service (NHS) and noncommercial institutions. These include guidance documents for research from the British Medical Research Council (MRC), the Department of Health (DOH) and the General Medical Council (GMC). The MRC have their own GCP guidelines [17] in which ICH GCP is used as a starting point, although the guidelines differ in some important aspects from ICH GCP guidelines. In addition, the MRC have published a document called *Good Research Practice* [18], which provides guidance in the scientific and ethical principles. The Research Governance Framework for Health and Social Care [12] sets out the standards to be applied to all research in the DOH while the GMC have provided guidance detailing best practice for doctors involved in research [19]. Until the European Commission has published guidance on the exact nature of the GCP to be adopted for the EU Directive, it is difficult to gauge the impact of the new Directive over and above that of the MRC GCP guidelines, and DOH and GMC Research Guidance documents. However, once the EU Commissioners have produced their GCP guideline, it will take precedence over any pre-existing national guidance.

Clinical pharmacologists working in the UK National Health Service (NHS) governed by the various research governances will see few fundamental changes but an increased emphasis on quality systems. One fundamental change will be the need in studies with healthy volunteers in the UK to have authorization from the Medicines Control Agency (MCA) as well as the present
requirement of a favourable ethics committee opinion before the start of the study [20]. The constraints of studies in patients in the NHS will still be present with the flow of various documents and costs to the Research and Development Directorate and management approval from the NHS Trust. Specific timescales for ethical review may help reduce some of the delays experienced in the past but stricter standards for the manufacture of study drugs and inspections by the MCA will add to the burden of research. The emphasis on quality systems to comply with the EU Directive will mean more and better training in GCP and the availability of Standard Operating Procedures.

Conclusions
A pessimistic approach to the imposition of GCP is one of slow strangulation of research particularly non-commercial research as more paper is produced. GCP and the new EU Directive would appear to some as ‘red tape’. Certainly, the EU legislation will be a challenge where resources are strictly limited and dependent on financial support from government agencies with limited budgets. However, there should be improvements in the quality of the data and better protection of the patient. Whether the disadvantages of GCP can be offset by the use of modern computer technology, and by fewer, but better planned and simpler studies, is open to debate. GCP will lead to data from clinical trials that are more acceptable both for publication, and for submission to health authorities to support a new treatment.

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