RESEARCH METHODOLOGY

Clinical trials: towards good practice

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Quality control, quality assurance, and audit are now an integral, though not always welcome, part of our daily lives. For many years the conduct of clinical trials has relied heavily on trust and the integrity of those involved, and the amount of regulation has been minimal. The introduction of the Declaration of Helsinki in 1964 spelt out the ethical considerations but further changes over the last decade with the introduction of the principles of good clinical practice (GCP) into clinical trials have seen a move towards much closer regulation. References to GCP in this paper relate to research practice in clinical trials and this topic will be examined further in the context of the introduction and implementation of the recent European Community guidelines.¹

The initiatives for the introduction of good practice into clinical trials have come from a variety of sources (originally the Food and Drug Administration in the United States, followed by the pharmaceutical industry worldwide, and the European Community). In the UK guidelines were first produced in 1988 by the Association of the British Pharmaceutical Industry (ABPI).² These guidelines were subsequently adopted voluntarily by the UK pharmaceutical industry. Some European countries then followed with their own version of GCP guidelines, for instance the Nordic Group in 1989.³ It is interesting, however, though there appears to be no clear explanation for the fact that while the ABPI refer to 'good clinical research practice' and the Nordic Group to 'good clinical trial practice', the European Community guidelines drafted subsequently by the Committee on Proprietary Medicinal Products³ just refer to 'good clinical practice'. These guidelines were approved in July 1990 and became effective on 1 July 1991.

The introduction of national legislation in support of GCP has been gradual throughout Europe and, not surprisingly, there remains some confusion over its status and also some variation in how it is regarded between America, Europe, and Japan. Similarly, there is considerable variation from country to country in sanctions which can be imposed for non-compliance. There are, however, hopes that there can be some standardisation and moves have already been made in this direction.

The introduction of GCP in the UK is based on the European Community guidelines.

There is a danger that the omission of the words 'research' or 'trial' may lead to confusion between good clinical *practice* and good clinical *care*, that is the doctor-patient relationship. So, within the guidelines GCP is defined as 'a standard by which clinical trials are designed, implemented and reported so that there is public assurance that the data are credible, and that the rights, integrity and confidentiality of subjects are protected'. The guidelines elaborate on how this might be achieved but, in general terms, GCP may be viewed as a gold standard or yardstick for the conduct of clinical trials, which should help to raise standards and also facilitate comparison of clinical trial results. Alternatively, the guidelines might be viewed as a set of management procedures designed to prevent mistakes and fraud and thereby protect the rights of the subject. Fundamental to the concept of GCP is the need for pre-established and systematic written procedures for the organisation, conduct, data collection, documentation, and verification of clinical trials. By means of a carefully documented 'audit trail' GCP provides a means of showing that what is claimed has actually been carried out.

Sceptics, or busy clinicians, may view the introduction of GCP as yet one more unnecessary hurdle to detract from their normal clinical way of working, and yet another example of excessive bureaucracy which is gradually stifling creativity. Others who see it very much as an imposition from within the pharmaceutical industry may feel threatened or aggrieved at the implied lack of trust, as well as concerned by the seemingly excessive demands.

So why is GCP needed in clinical trials? The protection of the subject is paramount and in this respect the guidelines may be viewed as an extension and reinforcement of the Declaration of Helsinki. The safety of the subject, particularly, when using hitherto untested drugs, must be ensured as far as possible. Human beings are not infallible and there must also be assurance about the conduct of clinical trials in terms of an attempt at elimination of cheating, fraud, or accidental error. Problems of poor study design must be avoided. There must be a standard for comparison of trial results given the diversity of settings in which clinical trials operate. This is particularly important in multicentre and multinational trials given the number of personnel and institutions involved.

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There is a need for a well defined process for the conduct of clinical trials, with which all participants are familiar. Waste of both human and financial resources as a result of poorly run trials must be avoided. The need for an audit trail has already been mentioned but it is not now enough to claim accurate data, there must be proof of accuracy. Finally, and this is one of the original aims of the guidelines, the conduct of trials to conform with GCP is designed to ensure a standard to facilitate regulatory submissions.

It is true that the guidelines, as originally conceived, were directed primarily towards the pharmaceutical industry and others involved in acquisition of clinical data for regulatory submissions for medicinal products. The scope of this article does not allow for detailed examination of the contents of the guidelines but they set out clearly the key parties and components involved in implementing GCP to that end. The three main parties are thus identified as: the sponsor, the monitor and the investigator, and the respective responsibilities, both clinical and for data handling, are clearly identified. Issues concerning the protection of subjects are covered through the sections on ethics committees and informed consent. The importance of statistics and quality assurance are also included, while the annex covers some practical aspects for implementing the guidelines.

A number of important elements are identified. The use of standard operating procedures (SOPs) to document all areas of activity and for standardisation of processes is an essential part of GCP. The SOPs are function specific but must specify individual responsibilities within the function and cover such areas as protocol preparation, reporting of adverse events, archiving, laboratory procedures, etc. Adapting to a life regulated by SOPs may be just one of a number of culture changes required if trials are to be run to GCP standards.

One of the most frequent criticisms of the introduction of GCP is the mass of paperwork that seems to be generated. Investigator handbooks and case report forms several inches thick are cited frequently, and they in turn generate demands for additional research staff to cope with the extra workload.

The need for a documented 'audit trail' does, however, mean that full and accurate records must be kept. It is no longer sufficient to claim results which cannot be fully supported. The guidelines also contain clear guidance on matters such as archiving of records. An extension of the 'audit trail', and a means of 'proving' accuracy of data is the need for verification of data contained in case report forms with the original source record. This may have considerable implications not only in terms of time but also for the confidentiality of the subject, and suitable arrangements must be made to ensure that this is safeguarded.

Largely because of the mass of documentation required to audit and give written proof at all stages of the clinical trial, the implementation of GCP does have significant implications for time, staff, and finances. It is crucial, there-

fore, that all involved in running a clinical trial to GCP standards, are fully aware *before* embarking on the trial that they can meet the demands. For instance, as large amounts of data are likely to be required on the case report forms it may be useful to have a research nurse available to complete the forms. GCP demands good communication between all parties involved, and also a more formalised way of working than people may be used to. The introduction of a culture change may require careful handling in order to convince everyone involved of the benefits of the required changes.

While the guidelines seem to specify a great deal of detail about some areas of trials work, they are quite vague about others and are, therefore, reasonably open to interpretation. This goes some way to explain the variations to be found even within the pharmaceutical industry. The guidelines do, therefore, offer some flexibility and, in terms of their practical application, can be adapted to suit individual circumstances.

As has already been stated, the guidelines on GCP were introduced originally for use in drug trials where regulatory submission was the main aim, and they are not entirely applicable to all types of evaluative and other research. The costs and time involved in running *all* clinical trials, not just those sponsored by the pharmaceutical industry for regulatory submission, to full GCP standards are probably prohibitive. There are none the less some elements of GCP which could, and should, be increasingly applied to all trials in order to avoid a major discrepancy in standards between drug registration trials for which full GCP is required and others for which registration is not an issue but for which credibility of trial data still is.

A fundamental principle of GCP is what have we done and how can we show we have done it? Trials must now be run to GCP if the results are to be credible and acceptable to others. The interpretation of the guidelines does offer some flexibility of interpretation but the implementation of GCP should really be seen as a matter of doing everything possible to ensure that clinical trials are conducted properly, as outlined in the guidelines, and that must surely be the aim of all involved in clinical trials? We must be able to say that we are running our clinical trials better than five or 10 years ago, and we need to be constantly reviewing the way they are run.

One might ask whether GCP actually results in better trials. In view of the effort involved in running a trial to GCP standards, it might be nice to think that the answer is yes. It is probably more realistic to say not necessarily, though it does certainly help to ensure a better quality of data and, for those trials involving new drugs, it will lead to quicker and easier drug registration. It also helps to ensure that all involved in a trial know who is responsible for what, and why, and the time frame in which tasks will be undertaken. It may also be seen to lend credibility to the claims of individual

investigators and should also help to ensure that fraud becomes ever more difficult.

It is absolutely vital, however, that a pragmatic approach is taken to the incorporation of GCP into trials if the end result is not to be counterproductive. The annex to the guidelines is designed to provide guidance on some of the practical aspects but it is perhaps better to think of applying the *spirit* of GCP to clinical trials, rather than aiming for slavish adherence to a complex set of rules. What is needed is a sensible, workable, and affordable interpretation, one which draws on the positive aspects but does not become entrenched too much in the minutiae. There has to be a balance between quality of data and the time/cost factor involved. There are already signs that, having initially embraced GCP wholeheartedly, the pharmaceutical industry is now beginning to ask questions about whether GCP is costing too much and is reviewing its original literal interpretation of the guidelines. Some streamlining may well be necessary in the hope of finding and maintaining the correct balance.

The practical implementation of any change in practice is a lengthy process and GCP cannot be achieved overnight. But, it is here to stay and as a principle for conduct of clinical trials it is something that we should all be aiming towards.

- 1 Committee for Proprietary Medicinal Products. Good clinical practice for trials on medicinal products in the European Community. *The rules governing medicinal products in the European Community. Vol III. CPMP, Addendum July 1990: 57-98.* (Catalogue No CB-59-90-936-EN-C.)
- 2 Association of the British Pharmaceutical Industry. *Guidelines on good clinical research practice.* ABPI, 1988.
- 3 Nordic Council on Medicine. *Good clinical trial practice: Nordic guidelines.* Nordic Council on Medicine, December 1989. (NLN Publication No 28.)

Commentary

THE GOOD CLINICAL PRACTICE GUIDELINES :

'GOOD' FOR THE PRACTICE OF CLINICAL TRIALS?

Over the past few years, concerns about actual or potential scientific fraud have prompted suggestions for the closer regulation of randomised controlled trials (RCTs) within good clinical practice (GCP) guidelines, as described in the paper by Ablett. She concludes that 'as a principle for the conduct of clinical trials it is something we should all be aiming towards'. While acknowledging that, in general, the guidelines are welcome, and indeed many of the suggestions have already become part of trial management, the aim of this commentary is to discuss whether applying them in practice is necessarily the way forward in all circumstances. The particular case of data monitoring in large 'pragmatic' trials is considered.¹

BACKGROUND

There are many versions of GCP. Ablett gives five references from 1988 to 1993 and points out some of the differences between them. For this commentary, the most recent version issued by the International Conference on Harmonisation (ICH) in June 1996 will be

used.² Clearly there will (and should) be many further versions of the details, but the basic principles are unlikely to change so often. According to this version, GCP is: 'an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are consistent' (page S4).

The guidelines were developed principally for use in explanatory drug trials sponsored by the pharmaceuticals industry: 'The objective of this ICH GCP Guideline is to ... facilitate mutual acceptance of clinical data by regulatory authorities' (page S4).

The practices suggested are already in common use in phase I and II drug trials, but the guideline goes on to state that: 'The principles established in this guideline may also be applied to other clinical investigations ...' (page S4). It is possible that the application of these guidelines may be less appropriate (or even have negative effects) in the particular circumstances of pragmatic trials.

EXPLANATORY AND PRAGMATIC TRIALS

Most phase I and II drug trials are explanatory trials which try to answer the question about whether or not interventions *could work*. In contrast, pragmatic trials are defined as those in which the aim is to evaluate the effectiveness of interventions in health care in their real world settings to answer the question *do they work*? Characteristically, pragmatic trials recruit large numbers of subjects (often necessitating international collaboration). This level of recruitment is facilitated by broad entry criteria (reflecting the state of clinical uncertainty at the time), simple procedures, minimal case report forms, and hard endpoints such as death. For example, the OSIRIS trial evaluated the effectiveness of different regimens for the use of a neonatal surfactant in terms of death and respiratory morbidity.³ Using a two page case report form, the trial recruited 6774 newborn babies from 229 centres in 21 countries, and was able to provide very precise estimates of effect. Pragmatic trials are more common for phase III or IV (post-marketing) drug trials, or trials of non-drug interventions such as new technologies, surgery, and other managements in the health services.

Although the explanatory and pragmatic perspectives are complementary, pragmatic trials try to disturb on going clinical practice as little as possible, other than in respect of the intervention(s) under investigation. Hence any major disruption to that usual practice could create problems in the interpretation of the results. Rigid adherence to some of the practical implementation of the GCP guidelines may be therefore be incompatible with the spirit of such trials. This can most clearly be seen in relation to the role of the trial monitors.

MONITORING

The term 'data monitoring' is used in two main ways. The first is applied to the work of independent safety or data monitoring committees (DMCs) whose role is to consider the ethics of continuing recruitment into a trial. Their recommendations are usually based on seeing accumulating trial data subdivided by random allocation.

In the current context, however, data monitoring is about monitoring the process of eliciting, processing, and analysing data in such a way that the rights and wellbeing of patients are protected, and that the information reported is as accurate, understandable, and credible. In the GCP guidelines, it is expected that the monitor(s) will visit and sometimes stay on site before, during, and after the trial. Seventeen responsibilities for monitors are listed, including for example, checking the accuracy and completeness of the case report forms, source documents, and other trial related records against each other.

The aim of this activity is to produce data that is not only of high quality, but also seen to be of high quality. The remainder of this commentary discusses some of the negative implications of this approach, and makes suggestions for adaptations which might be more suitable for pragmatic trials.

Intensive on site data monitoring (1) may not be so appropriate for large pragmatic trials, (2) is expensive, and may have unintended and harmful side effects principally by (3) altering clinical practices, and by (4) decreasing recruitment.

(1) Although scientific fraud doubtless exists, it is most likely to occur when its perpetrator is able to profit either financially or professionally. There is little incentive for this in large multicentre pragmatic trials where the end result is a corporately authored paper. Even if a particular individual in a centre was fraudulent, his or her activities would be extremely unlikely to lead to misleading results, as this contribution would be small in relation to the overall trial data.⁴ A similar argument about the lack of scientific importance of a small number of genuine mistakes also applies. Of course, such practices are clearly not to be encouraged, but they may not have any material effect on the trial results. Thorough quality control in the data coordinating centre, perhaps combined with on site data checking based on sampling techniques (whether random or targeted), would probably detect both fraud and errors if they were to happen often enough to be unacceptable.

(2) Intensive data monitoring is expensive. This has implications for the agencies which fund trials. Although accepted in many drug company sponsored trials, the costs for such monitoring are less commonly requested from the research councils and other publicly funded bodies. At a time of financial stringency, they may be more reluctant to provide such funds. If intensive monitoring makes it more difficult to get funding to do trials, patients will be the losers. Also, intensive monitoring is not just

expensive for the sponsors, but is also costly in terms of the time of busy clinicians. This may discourage some potential collaborators from joining in a trial wholeheartedly (see point 4 below).

(3) Pragmatic trials aim to reflect the real world of clinical practice. Currently, this does not include on site monitoring. Such intrusiveness (actual or perceived) may influence other aspects of clinical practice and so make it harder to generalise the results of the trial to centres in which such monitoring is not routine.

(4) Finally, and most importantly, in order to answer important clinical questions reliably, a sufficiently large numbers of patients must be recruited. It is likely that intensive monitoring will be seen as a barrier to recruitment. Clinicians may resent being treated as potential delinquents. Following GCP guidelines in this respect may produce high quality data for a small number of patients from a small and unrepresentative number of centres.

As Ablett suggests, the potential problems lie not so much with the principles of GCP, as with slavish adherence to them in practice. Such adherence is an unevaluated intervention, in much the same way as many other interventions in health care, and current opinions about its advantages and disadvantages are highly speculative. The likely trade offs of quality against precision need to be assessed. The onus must be on the proponents of GCP to show that they do more good (in terms of increasing public confidence and reducing the risks that fraud and mistakes will produce significantly misleading results) than harm (in terms of reducing the chances of important trials getting funded or making recruitment so difficult that it becomes harder to provide precise estimates of the effects of interventions). The aim of conducting RCTs in the clinical setting is ultimately to improve the care provided to patients by finding out whether interventions are (cost) effective. This central consideration needs to be kept high on the agenda when discussing the means whereby the aim is translated into research practice in the context of RCTs, so that the ends may be served by the means, rather than driven by them.

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- 1 Schwartz D, Flamant R, Lellouch J. *Clinical trials*. London: Academic Press, 1980.
- 2 International Conference on Harmonisation. Tripartite guideline for good clinical practice. *Good Clinical Practice Journal* 1996;3:4 (suppl).
- 3 The OSIRIS Collaborative Group. Early versus delayed selective administration of a synthetic surfactant—the judgement of OSIRIS. *Lancet* 1992;ii:1363-9.
- 4 Peto R, Collins R, Sackett D, et al. The trials of Dr Bernard Fisher: a European perspective on an American episode. *Controlled Clinical Trials* 1997;18:1-13.