Academic clinical research in the new regulatory environment

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ABSTRACT – As a result of European legislation passed in 2001 (Directive 2001/20/EC), all clinical trials, whether sponsored by industry, a major national body or charity, or done by a single academic investigator, must get approval from the Medicines and Healthcare products Regulatory Agency (MHRA) as well as obtaining ethical approval. This requires all studies to be carried out to the standards of 'Good Clinical Practice' and places burdens on investigators in terms of reporting adverse events and archiving. A new directive has been published in draft form that will finally define what is meant by Good Clinical Practice in Europe.

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It is 40 years since the first major piece of European medicines legislation came into being. This was Directive 65/65/EC[1] which set out the framework within which member state governments had to regulate the development and approval of medical products in their countries. The response to this Directive in the UK was to introduce the Medicines Act 1968, which has been the mainstay for all UK medicines legislation ever since.

This, and all subsequent legislation until 2001, applied mainly to work carried out by the pharmaceutical industry rather than to academic work.

Thus, all clinical trials on products not on the market had to be approved under what was known as a CTX. This was in fact an exemption from the need to hold a Clinical Trial Certificate. Data were submitted to the agency (now the Medicines and Healthcare products Regulatory Agency (MHRA)) along with the proposed protocol. The doctor working within the company signed to say that they were taking the responsibility for the trial based on the information available, and the agency would intervene only if they felt either that the manufacturing data cast doubt on the quality of the product or that the pre-clinical safety tests indicated too high a risk of unacceptable side effects in the subjects.

Clinical pharmacology studies in healthy non-patient volunteers were not included in this process, as the Act required that there should be potential 'benefit' to the subjects of the trial in order for it to be regarded as a clinical trial. Ethics committee approval was required but not government approval.

Academic investigators were required to get permission to carry out studies by submitting what was known as a doctors' and dentists' exemption certificate (DDX), which gave the manufacturer permission to supply material for a clinical trial without taking any responsibility for the design or conduct of the study themselves.

One of the problems of Directive 65/65/EC was that whilst it provided a general framework for the activity of pharmaceutical companies, there was no specific guidance on what government-approved processes were required to authorise clinical trials in the various member states. Thus it was possible to conduct trials in Germany without any governmental approval, whether they were clinical pharmacology studies or therapeutic trials, whilst in Spain it took nine months to get permission to do any study at all.

This, plus the fact that Europe seemed to be becoming less attractive than the USA to companies conducting studies, led to the idea of harmonising the processes for authorising clinical trials across the EU.

The new legislation

In 2001, the European Union enacted a new Directive (2001/20/EC)[2] which had as its objective the harmonisation of clinical trial approval across the EU. The Directive is only 22 pages long and seems at first sight an innocuous document. There are, however, a number of problems in the detail and the implementation. The first is that the Directive is backed up by a series of guidance notes designed to help with the interpretation of various elements within the Directive and to guide member state governments in the drafting of the local national legislation that transcribes the Directive into national law. This process in itself is problematic. Because it is a Directive, it is open to interpretation and allows the possibility that national governments will emphasise different aspects of it. Thus there is a risk that there will be as much disparity as there was before, and this is exactly what has happened.

From the point of view of the UK, the Directive made two fundamental changes:

- all clinical trials carried out by pharmaceutical companies now needed to be approved by the MHRA, including phase 1 or clinical pharmacology studies
- studies carried out in academia and not sponsored by pharmaceutical companies would be subject to the same regulations.

In addition, the Directive did not define what was meant by 'Good Clinical Practice' (GCP). This may sound strange, but there are several versions of 'Good Clinical Practice', some more prescriptive than others. There was therefore the prospect of new legislation coming into being which would mean amending national legislation which had just been enacted, and national governments were left to second guess what was coming. The promised Good Clinical Practice Directive[3] is now in draft form but because it has to go through all the internal EU processes its final form is still uncertain. In fact, on first reading, this is not really a directive on GCP, but more an exercise in providing guidance notes for the Directive where they had previously been omitted.

It was against this background that the UK Government introduced the Medicines for Human Use (Clinical Trials) Regulations which came into force on 1 May 2004. At 86 pages, the Regulations are almost four times longer than the Directive. The UK has a history of making strenuous efforts to ensure that it implements both the letter and the spirit of EU legislation. The Regulations are difficult to read as there so many cross references, so the MHRA published *Description of the Medicines for Human Use (Clinical Trials) Regulations 2004*[4] and it is this document that gives most people the information they need to work within the new environment. It covers all the areas that need to be considered when setting up a clinical trial.

Ethics committees have always been pivotal in the clinical trial process, but the way they should be structured and run, as well as the scope of their responsibilities, is more clearly spelt out. The legislation provides for the establishment of the UK Ethics Committee Authority. There was provision in the Directive for a system of ethics committees but, as with so many aspects of the Directive, it was not defined, and this was the UK's response to the need for a national system for ethical approval of clinical trials. There is now a single ethics form for all studies. This might seem helpful in that familiarity could lead to ease of use, but as the form is trying to cater for everything from a simple comparative study between two well established products to a complex gene therapy trial, in practice it has proved to be problematic for many people.

The process for obtaining approval to start a clinical trial is described and this is essential reading as this now applies to all. Figure 1 sets out the procedures that need to be followed.

There are sections on good clinical practice and drug safety – 'Pharmacovigilance'. There is a section on manufacturing and importation, and one on the labeling of clinical trial material. The final specific section is on inspection and enforcement. It is worth remembering that this legislation comes under the criminal law and there are criminal penalties for not following the provisions contained within it.

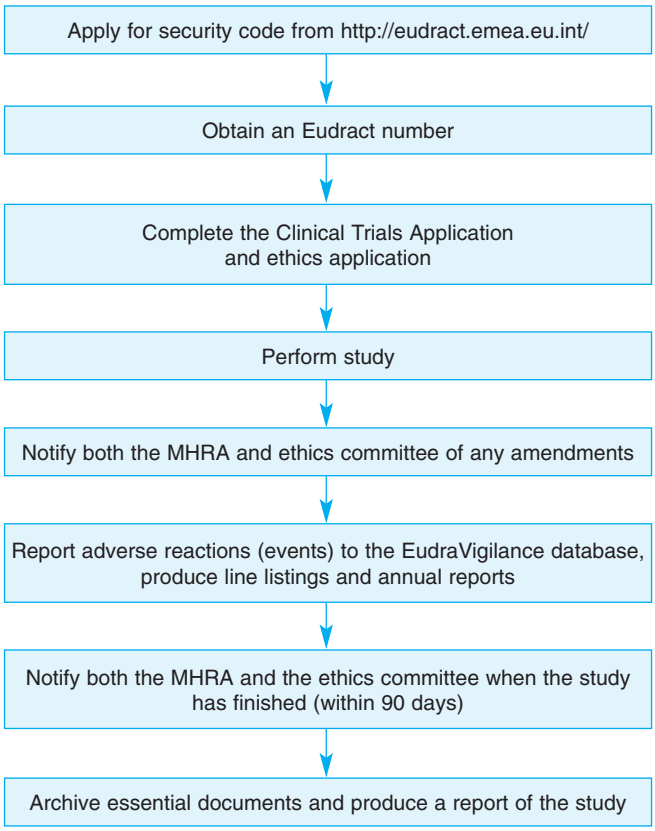

Fig 1. Procedures to be followed in order to obtain approval for a clinical trial. Eudract = EU clinical trials database on which all studies are recorded; EudraVigilance = EU database for adverse events; MHRA = Medicines and Healthcare products Regulatory Agency.

What are the problems?

If a clinical trial is being conducted as part of a pharmaceutical company programme, then there is little or no change. The company will have adapted its processes and procedures to accommodate the new legislation. The same will largely be true for studies by the large national charities. It is those studies that are carried out by individual researchers that are most dramatically affected. Both the EU Clinical Trials Directive and the draft Good Clinical Practice Directive talk in terms of exempting academic investigations from certain aspects of the legislation, but only in the areas of manufacturing and labeling to date.

The first issue is the need to define who has what role within the trial. The concept of the 'sponsor' is key and this may be the same person as the investigator. The sponsor is someone who takes responsibility for the initiation, management and conduct of the trial. These responsibilities are serious as they include an undertaking to report information, including safety data, as defined in the Directive. It is not necessary for the sponsor to be the investigator, but they may be the same person in small

studies that are not sponsored by a company or a national charity.

One of the difficulties for investigators is to understand and comply with their responsibilities for reporting adverse events. The requirements themselves and understanding what needs to be reported may both cause problems, partly because of the language used. The requirements, as defined in the Clinical Trials Directive, are as follows:

- *The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.*
- *Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.*
- *The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.*

These are the general requirements and, as can be seen, they place a heavy burden on the individual investigator, and more so if this person is also the sponsor.

In addition, there are some prescriptive time limits on reporting adverse events:

- *The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.*
- *All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.*

Finally, there is a requirement to inform the ethics committee of all adverse events that have happened in the previous twelve months.

Thus, in a clinical trial of a beta-blocking agent versus an ACE inhibitor in hypertension for example, each and every minor cough and episode of cold limbs would have to be recorded as adverse events and reported on an annual basis.

The other major problem for investigator-led studies is in the product itself. If it is used as manufactured by the company that markets it then there is no problem. But as soon as any changes are made to the presentation by way of encapsulation of tablets to make them double blind, then the Good Manufacturing Practice (GMP) legislation comes into play and someone known as a 'Qualified Person' is required. This is an individual, usually but not always a pharmacist, who has the appropriate training and skills in GMP to oversee adherence to these regulations.

These are the three key areas that anyone planning a clinical trial needs to consider. They are likely to be problematic for individual investigators, and may increase the tendency to seek sponsorship from a pharmaceutical company to help with the extra resources needed. Thus, there is the risk that the number of purely academic studies will go down and reliance on industrial sponsorship will go up.

Conclusions

The new legislation enacted in the UK places a burden on individual investigators that may deter them from doing studies without the support of either a pharmaceutical company or a large charity. This may not be in the best interest of either academia or industry. For example, studies on old drugs that may throw new light on the best way to use existing therapies may not be carried out. Whilst the general thrust of the legislation, such as Good Clinical Practice and proper ethical approval, must be applauded, some aspects of it seem over-burdensome and will do little to add to public health.

References

1 Council Directive 65/65/EC. *Official J Eur Union*, 26 January 1965.
2 Directive 2001/20/EC of the European Parliament and of the Council. *Official J Eur Union*, 1 May 2001.
3 Draft Commission Directive on Good Clinical Practice (2004).
4 Medicines and Healthcare products Regulatory Agency. *Description of the Medicines For Human Use (Clinical Trials) Regulations 2004.* London: MHRA, 2004.