EU DIRECTIVE ON GOOD CLINICAL PRACTICE IN CLINICAL TRIALS
DH & MHRA BRIEFING NOTE

Purpose

1. The Clinical Trials Directive 2001/20/EC heralds certain additional responsibilities for the Medicines and Healthcare products Regulatory Agency (MHRA), for ethics committees and for those running or supporting clinical trials of medicines. This note (which does not provide an exhaustive list of the Directive’s requirements) has been produced by the MHRA and the Department of Health (DH) to inform interested parties, in particular those in the public sector, of impending changes under the Directive. It addresses some frequently asked questions about transposition of the Directive into UK legislation. The MHRA is the primary source of authoritative advice and information about the Directive in the UK. Guidance from the European Commission about the requirements in the Directive is now under consultation, see Annex A for further details.

Background


3. Agreement on the Directive was reached in February 2001 and the final text was published in the Official Journal of the European Communities on 1 May 2001. A link to the appropriate Internet page is available from the MHRA website. Member States have until 1 May 2003 to draw up legislation implementing the Directive, although application of the requirements may be delayed until 1 May 2004. The necessary UK implementing regulations are now being prepared and will be published for consultation in due course.

Scope of the Directive

4. The scope of the Directive is wide. It covers the conduct within the EU of clinical trials on medicinal products (as defined in Directive 2001/83/EC on the Community Code relating to medicinal products for human use) involving human subjects. The term “medicinal product” hinges on whether it is medicinal by function, or whether it is presented as treating or preventing disease in human beings. In effect, every clinical trial on medicinal products (aside from non-interventional trials – see paragraph 6) will be covered, whether sponsored by industry, Government, research organisation, charity or university.
5. The Directive sets standards for protecting clinical trials subjects, including incapacitated adults and minors. Importantly, it will also require Member States to establish ethics committees on a legal basis and impose legal obligations in relation to certain procedures, such as times within which an opinion must be given. In addition, it covers certain Licensing Authority procedures for commencing a clinical trial. It lays down standards for the manufacture, import and labelling of investigational medicinal products (IMPs) and provides for quality assurance of clinical trials and IMPs. To ensure compliance with these standards, it requires Member States to set up inspection systems for good manufacturing practice (GMP) and good clinical practice (GCP). It provides for safety monitoring of patients in trials, and sets out procedures for reporting and recording adverse drug reactions and events. To help with the exchange of information between Member States about approved clinical trials and pharmacovigilance, secure networks will be established, linked to European databases.

6. The Directive’s provisions do not distinguish between commercial and non-commercial clinical trials (ie those conducted by academics without the participation of the pharmaceutical industry). However, non-interventional trials are not within the scope of the Directive, ie those where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation – see definition at Article 2(c). In these cases the assignment of a patient to a particular therapeutic strategy is not decided in advance by a trial protocol, but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the patient in the study. Also, no additional diagnostic or monitoring procedure related to the therapeutic strategy is applied to the patients and epidemiological methods are to be used for the analysis of the collected data.

Implications for clinical trials conducted in the UK

7. Transposition of the Directive’s requirements into national legislation will be informed by the European Commission guidance presently under consultation. Most of the procedures and criteria are already part of current UK clinical trials practice. However, when fully implemented, the Directive will lay down significant new controls which will affect clinical research and development of medicinal products in the UK, including in the NHS, in the following areas:

- specific timescales for ethics review (see paragraph 17)
- a requirement for approval of phase I clinical pharmacology studies on healthy volunteers (see paragraph 21)
- the manufacture of IMPs only at licensed manufacturing sites under GMP conditions (see paragraph 24)
- the introduction of inspections to assess compliance with GMP and GCP at sites (industry, hospitals, universities and other areas which are involved in clinical trials of medicinal products) (see paragraph 27)

8. These and other key issues are explored in more detail below.
Children and incapacitated adults

9. The Directive pays special attention to the ethical conduct of clinical trials in which children and incapacitated adults participate. The current criteria for conducting clinical trials in incapacitated adults are set out in the internationally agreed guidance on GCP\(^1\) that has been applied in Europe since 1997. Similarly, internationally agreed guidance on conducting clinical trials in children\(^2\) came into operation in Europe in January 2001. Articles 4 and 5 will have the effect of laying down similar requirements. The MHRA understands that the intention of the wording of the Directive in relation to clinical trials in children and incapacitated adults is similar to the intention of the wording in the current guidance. For these reasons we do not believe that it will prevent ethical research into diseases that cause incapacity or diseases of children.

Informed consent

10. The Directive sets out requirements for consent processes, although it is understood that these are largely already regarded as good practice in the UK. Articles 4 and 5 of the Directive deal respectively with informed consent for minors and for incapacitated adults not able to give informed consent. A “legal representative” may act for a trial subject where the person is not able to give informed consent. The “legal representative” may be interpreted by Member States in line with pre-existing national arrangements. Under the law of England and Wales, a person with parental responsibility may in certain circumstances give consent to the medical treatment of a child; in the case of incapacitated adults, treatment is generally lawful if the treating doctor determines that it is in the best interests of the patient. Different arrangements apply under Scottish law. Although in general the intention is that these arrangements should continue after implementation of the Directive, consideration is being given to the most appropriate approach in implementing the requirements concerning a legal representative in respect of incapacitated adults in England, Wales and Northern Ireland.

11. Article 3 requires all trial subjects, or the person’s legal representative if the subject is not able to give informed consent, to be given an opportunity in a prior interview to understand the objectives, risks and inconveniences of the trial, the conditions under which it is to be conducted, and to be informed of the right to withdraw at any time. Consent must be written (where the patient is unable to write, oral consent must be obtained in the presence of at least one witness).

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\(^1\) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
\(^2\) Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)
Sponsor

12. The term “sponsor” is defined in Article 2 as “an individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial”. A number of provisions require the sponsor to undertake particular actions. For trials undertaken in the NHS, the Directive’s requirements need to be seen alongside the responsibilities of the sponsor as set out in the Research Governance Framework for Health and Social Care (published on the Department of Health website) which will continue to apply after implementation of the Directive. The Commission’s guidance on the principles of GCP would indicate that the sponsor will be able to use a contract research organisation or other body to carry out trial-related activities on their behalf.

Application of GCP

13. The Directive requires Member States to apply the principles of good clinical practice covering the design, conduct, recording and reporting of clinical trials. It also requires the Commission to publish detailed guidance. The International Conference on Harmonisation (ICH) guidelines on GCP currently set the standards for conducting clinical trials to support product registration in Europe, USA and Japan. The guidance from the Commission on GCP sets out essentially the same principles set in the context of the Directive. The GCP guidance also sets out the contents of the clinical trial protocol and investigator’s brochure.

Risks and benefits

14. The Directive specifies that a clinical trial should only take place where the foreseeable risks and inconveniences have been weighed against anticipated benefit for the individual trial subjects, and other and future patients. It will be for the ethics committee and/or competent authority to consider this requirement before approval is given. The Directive recognises the need for clinical trials in children to improve the treatment available to them and for paediatric medicines, including vaccines, to be tested scientifically before widespread use.

15. Similarly, the Directive recognises the need to conduct clinical trials on persons incapable of giving their consent, such as persons with dementia. The informed consent of the 'legal representative' must be obtained, and the person incapable of giving consent must be informed according to his/her capacity for understanding (see paragraph 10 et seq). Concerns were raised about vaccines trials for Alzheimer’s disease and whether this would be possible under the provisions regarding subjects who are not able to provide valid consent. The Directive permits the inclusion of incapacitated adults not able to give informed legal consent where “there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or producing no risk at all” (subparagraph (i) of Article 5). These points are also picked up at relevant places in the guidance documents under consultation.
Indemnity/compensation

16. Article 3 states that a clinical trial may only be undertaken if (along with other requirements) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor. The obligations on the ethics committee (in Article 6 and in the guidance notes on application to the ethics committee) include consideration of the provision for indemnity or compensation in the event of injury or death attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor. The Directive does not require the provision of a specific compensation scheme for non-negligent harm to a participant from a clinical trial, and there are no moves to change the present arrangements in the UK for publicly-funded (eg MRC and NHS) trials where consideration will be given for ex gratia payment should such an event arise. For industry sponsored trials, the existing guidance and model indemnity agreement with the Association of the British Pharmaceutical Industry (HSC(96)48) remains, and it will continue to be the case that individuals or bodies may be liable in negligence if they breach the duty of care owed to trial subjects.

Ethics Committees

17. The Directive requires Member States to place specific responsibilities on ethics committees, including a 60-day time limit for decisions (Article 6(5)). It is envisaged that ethical review and Licensing Authority authorisation (see paragraph 18) will be able to take place in parallel. (Clinical trials of gene therapy, somatic cell therapy and all medicinal products containing genetically modified organisms are permitted certain extensions to the 60 day time limit for ethical and competent authority approvals; no time limit is imposed on ethics committees for consideration of xenogenic cell therapy trials.)

Pre-commencement authorisation and trial reports

18. Article 9 requires the sponsor to submit a valid request for authorisation to the Licensing Authority of the Member State in which it is planned to conduct the trial. The competent authority for the UK is the Medicines and Health-care products Regulatory Agency (MHRA), acting on behalf of the Licensing Authority under the Medicines Act 1968. The MHRA Clinical Trials Unit currently provides medicinal product trial authorisation through the Clinical Trials Exemption (CTX) scheme for the pharmaceutical industry and through the Doctors and Dentists Exemption (DDX) scheme for trials initiated by doctors or dentists.

19. When the new legislation is enacted, no clinical trial of a medicinal product for human use may commence in the UK unless:

- an application for authorisation has been made to the Licensing Authority and
- the Licensing Authority has not informed the sponsor of any grounds for non-acceptance within the applicable time period;
or, in the cases specified in paragraphs 5 and 6 of Article 9, unless:

- the prior authorisation of the Licensing Authority has been obtained (eg for products containing genetically modified organisms).

20. It is proposed that, in most cases, the time limit for consideration by the Licensing Authority will be 30 days, extendable to 60 days.

21. Currently, studies in healthy volunteers in the UK do not require regulatory approval and can commence after an ethics committee has given a favourable opinion. The Directive will require the submission to the Licensing Authority of an application for authorisation and a favourable ethics committee opinion before a healthy volunteer trial can commence. The information required, format and procedures involved for all such submissions are the subject of guidance, currently under consultation. MHRA has agreed to respond to a request for authorisation for a Phase I healthy volunteer study in an average of 14 days and no later than 21 days. Appropriate national targets will be set against which MHRA’s performance will be monitored and results published regularly.

22. Article 10 requires a report to the Licensing Authority and ethics committee at the end of the trial within 90 days of the trial’s conclusion. Provisions for the suspension or prohibition of a clinical trial by a competent authority are given in Article 12, while Articles 16 and 17 cover reporting of serious adverse events and serious unexpected adverse reactions. The detailed processes involved will be set out in the implementing regulations, which will take into account the Commission guidance currently under consultation.

23. The application to the ethics committee and Licensing Authority will need to include a reference number available from the EUDRATRACT database (on which information on all trials will be held for reference purposes); it is envisaged that there will be a simple web-based process to obtain this.

**GMP and IMPs (Good Manufacturing Practice and Investigational Medicinal Products)**

24. IMPs include placebos and active comparator products. In accordance with Article 13, their manufacture or importation from countries outside the European Economic Area (EEA) ie the 15 EU Member States plus Iceland, Liechtenstein and Norway, will require prior authorisation from the Licensing Authority for trials conducted in the UK. Essentially, preparation of IMPs will require compliance with standards equivalent to those for manufactured products at licensed sites, authorised via a manufacturer’s licence. The manufacturer or importer must follow GMP requirements and have available a 'Qualified Person' (QP) as defined in Article 49 of Directive 2001/83/EC. The QP has a pivotal role in ensuring that the products meet the specification approved for the trial and that they have been made in accordance with existing EU guidance on GMP.

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3 Rules and Guidance for Pharmaceutical Manufacturers and Distributors, MHRA 1997- Annex 13
“Manufacture of Investigational Medicinal Products”
Revisions to Annex 13 of the published GMP guide to take account of the Directive’s requirements on IMPs have been published. Labelling requirements will also be set out in this Commission guidance.

25. Article 13 permits a person carrying out the duties of a QP before the Directive comes into force (but who is not otherwise a "qualified person") to be authorised to continue those activities. How this will be administered in UK has still to be decided. However, it is understood that there is not likely to be a need for a Manufacturer's Licence and a QP to cover reconstitution and packaging of IMPs by, or under, the supervision of a pharmacist at a hospital for use in a clinical trial at that site.

26. It is not yet clear whether the number of sites able to prepare IMPs for clinical trials will remain the same as at present. It is likely that some sites already licensed to manufacture 'specials' may be suitable to be licensed also to manufacture IMPs.

GCP and GMP inspections

27. Provisions for inspection arrangements and appointment of inspectors by competent authorities are set out in Article 15. MHRA will charge for inspections, amount still to be determined. Inspection will include the trial site(s), manufacturing site, any laboratory used for analysis, and/or the sponsor’s premises. MHRA have formed a GCP inspection group, which has undertaken pilot inspections of volunteer sites in readiness for the Directive’s implementation. The Commission is consulting on guidelines on inspection procedures for the verification of GCP compliance and the qualifications of GCP inspectors. MHRA’s Inspectorate is willing to conduct on request voluntary inspections of sites in the UK involved in clinical trials, including sponsor sites (commercial and non-commercial), manufacturing and assembly sites, contract research organisations and investigational and laboratory sites before the Directive is implemented to help in preparation. MHRA is also willing to give general advice.

28. Statutory GCP inspections are likely to be of two types:

   i. cyclical, systems-based inspections of sponsors (commercial and non-commercial) and contract research organisations involved in clinical trials in the UK;

   ii. triggered inspections as required.

The sponsor/contract research organisation will be expected to meet the fee for cyclical systems-based inspections. MHRA are considering how often NHS sites will need to be inspected.
Consultation

29. As with all new legislation, there will be wide consultation on the proposed implementing regulations starting in autumn 2002. Those to be consulted will include the medical colleges, charities and organisations linked to particular diseases. All comments will be carefully considered before the legislation is finally agreed. The Government welcomes any comment that will help to ensure that people volunteering for clinical trials are properly protected and that the quality of the information obtained from the trials is of the highest standard.

Conclusion

30. The implementation of this Directive will have wide-ranging implications for arrangements concerning clinical trials to test medicinal products in humans in the UK. The UK Government’s objective in transposing the new requirements is to facilitate high standards of patient safety and clinical research without impeding progress. The same standards will apply in all other EU Member States. Commissioners and those undertaking research will need to take account of the new requirements in planning programmes of work involving medicines trials.
EUROPEAN COMMISSION CONSULTATION DOCUMENTS

The European Commission has published guidance and requirements concerned with the implementation of Directive 2001/20/EC. These documents were placed on its website at:

http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm

on 12 July, and are under consultation until 2 October 2002. The documents listed are also included on:

http://pharmacos.eudra.org/F2/pharmacos/docs.htm

and the address for comments is given as julia.dunne@cec.eu.int

The MHRA is in the lead in the UK and will be co-ordinating a UK view on the main documents in due course. MHRA would be pleased to receive copies of any comments sent to the European Commission, preferably by early September. These should be addressed to:

matthew.garland@MHRA.gsi.gov.uk

The relevant documents listed on the Commission’s website are (with elements of titles emboldened for ease of subject areas identification):

Detailed guidance on the **European database of Suspected Unexpected Serious Adverse Reactions** (Eudravigilance - Clinical Trial Module)

Detailed Guidelines on the **principles of good clinical practice** in the conduct in the EU of clinical trials on medicinal products for human use

Detailed guidance on the application form and documentation to be submitted in **application for an ethics committee opinion** on a clinical trial on a medicinal product for human use

Detailed guidance for the **request for authorisation of a clinical trial** on a medicinal product for human use **to the competent authorities** in the European Union, notification of substantial amendments and declaration of the end of a clinical trial

Detailed guidance on the **European clinical trials database** (EUDRACT Database)

Detailed guidance on the collection, verification and presentation of **adverse reaction reports** arising from clinical trials on medicinal products for human use

The same website includes other related documents on the implementation of the Directive. These were released earlier for consultation and some of the deadlines for comment have passed.