

## EU Clinical Trials Directive:

### Sponsorship responsibilities in publicly funded trials

#### *Medicines for Human Use (Clinical Trials) Regulations 2004*

##### Summary

- For every trial, someone must take on each of the sponsor's responsibilities.
- There is flexibility for anyone doing so, to make arrangements with others.
- The request for a Clinical Trials Authorisation (CTA) may allocate the sponsor's responsibilities among several organisations.
- Normally, the chief investigator will act on behalf of the main research employer for the trial when submitting the request for a CTA.
- Other options:
  - The request may be made on behalf of the main funder
  - The request may be made on behalf of the main trial site
  - An individual investigator may make the request as investigator-sponsor

Box 1

#### **Introduction**

1. Directive 2001/20/EC, relating to the implementation of Good Clinical Practice (GCP) for clinical trials of medicinal products, required Member States to adopt the laws, regulations and provisions necessary to comply with the Directive. On 1 April, the United Kingdom adopted implementing Regulations under the European Communities Act 1972, subject to Parliament.
2. This note<sup>1</sup> describes implications of the UK's approach to implementing requirements of the Directive concerning the sponsor, particularly in relation to collaborative publicly funded trials. First, it describes what is possible under the Regulations. Then it goes on to discuss some considerations that might help partners in publicly funded trials to decide who may be expected to take on sponsorship responsibilities in different circumstances.

#### **What is possible under the Regulations?**

- *For every trial, someone must take on each of the sponsor's responsibilities*
3. Under the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), no-one may start a clinical trial unless:
    - an ethics committee has issued a favourable opinion;

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<sup>1</sup> The note builds on conclusions of a workshop that contributed to a MRC/Department of Health project to codify good practice in publicly funded UK clinical trials with medicines. The Department is grateful for the contributions of those who took part in these discussions.

- the trial has been authorised by the licensing authority<sup>2</sup>;
  - the sponsor of the trial, or a person authorised to act on the sponsor's behalf, is established in the EU.
4. The EU Directive defined a sponsor as *an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial*. The EU Commission has yet to publish its understanding of the way the responsibilities of sponsorship may be allocated. Some details in this note could be affected by any EU-wide interpretation of the Directive.
  5. The UK Regulations define legal responsibilities sponsors must arrange to carry out. The main responsibilities are those in Box 2.

### Sponsor's main responsibilities under the UK Regulations

#### **Part 3: authorisation and ethics committee opinion**

- Request clinical trial authorisation (CTA), amend the request,
- Produce undertaking to allow inspection of premises in third countries if required
- Give notice of amendments to CTA, make representations about amendments
- Give notice of amendments to the protocol
- Give notice a trial has ended

#### **Part 4: Good Clinical Practice and conduct**

- Put and keep in place arrangements to adhere to GCP (if no other person is specified)
- Ensure Investigational Medicinal Products available to subjects free of charge
- Take appropriate urgent safety measures (with investigator)

#### **Part 5: pharmacovigilance**

- Keep records of all adverse events reported by investigators
- Ensure recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARS)
- Ensure investigators are informed of SUSARs
- Ensure all SUSARs including those in third countries entered into European database
- Provide annual list of suspected serious adverse reactions and a safety report

#### **Box 2**

6. For most trials of medicines for regulatory purposes (such as those leading to a marketing authorisation), the request for a Clinical Trials Authorisation (CTA) will identify one person<sup>3</sup> that takes on responsibility for all these duties.
7. It is typical of publicly funded trials that a group of partners make collaborative arrangements to initiate, manage and fund them. The Regulations allow the CTA to name more than one person that takes on the sponsor's responsibilities. The partners could choose to take joint responsibility. In that case, all of them would accept joint liability for all of the sponsor's responsibilities. The Regulations also allow a request for a CTA to name a group of partners, each taking on a set of

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<sup>2</sup> The Directive and UK Regulations relate only to clinical trials of medicinal products. The Medicines and Healthcare products Regulatory Agency (MHRA) is the licensing authority and competent authority for the United Kingdom. See the MHRA's web site for definitions of clinical trials and of medicinal products. The same principles of Good Clinical Practice apply to other clinical trials. See the MRC's web site for guidelines on applying these principles to other trials.

<sup>3</sup> That is, a single legal person or organisation.

sponsorship responsibilities, grouped by function<sup>4</sup>. As a group, they would collaborate to cover all of the sponsor's functions.

8. For a group covering the responsibilities of the sponsor, the CTA would specify which set of functions each of them is to take on: authorisation (Part 3 of the Regulations); GCP and trial conduct (Part 4) or pharmacovigilance (Part 5). Appendix A to these notes summarises how the Regulations enable a group to take on sponsorship responsibilities. Regulation 3 defines the term "sponsor" for these purposes.
  9. For each legal responsibility, for the purposes of the Regulations, the named person would be responsible for performing it. If the MHRA issues a CTA on the basis that another named person takes on a specified set of responsibilities, the main applicant would not be held liable under the Regulations for a breach of those duties<sup>5</sup>.
  10. The diagram at appendix B summarises how a group can allocate responsibilities in sets by function. For explanation, these notes use the term "co-sponsors" for members of a group who take on and allocate sponsorship responsibilities and duties among them, and do not accept joint liability for each responsibility. The term "co-sponsor" is not used in the EU Directive and is not in the Regulations.
  11. It is for the group to propose an allocation of responsibilities that enables them and others to conduct a particular trial within the law. For the request to be valid, it must show the MHRA that, between them, the "co-sponsors" take on all the sponsor's responsibilities. (Some responsibilities do not fall to a sponsor in particular but are general legal conditions<sup>6</sup>. The CTA may name other people with those responsibilities. In any case, the trial protocol is expected to describe a scheme of allocation specifying who will take on responsibility for the various arrangements across all the trial sites.)
  12. It is not within the intention of the EU Directive for the CTA to sub-divide the sponsor's responsibilities among many "co-sponsors". (For example, a request naming a different "co-sponsor" for each trial site would not be valid.) It would not be acceptable to divide the sponsor's responsibilities among "co-sponsors" geographically, or in other ways that allow individual "co-sponsors" to amend the protocol in isolation.
- *Flexibility to make arrangements*
13. In all these arrangements, there is flexibility. It is up to the person or organisation that takes on a set of responsibilities to make arrangements to carry them out. They may arrange for their employees to complete the necessary tasks. They may engage someone else to do so on their behalf, under an agreement or contract.
  14. For example, a commercial sponsor may contract with a Clinical Research Organisation. In publicly funded trials, a Clinical Trials Unit (CTU) is more often the means of carrying out many of the sponsor's responsibilities. It is for the partners to decide what status to give a CTU. They may decide the CTU will work on contract for a sponsor. Alternatively, the organisation employing the

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<sup>4</sup> See paragraphs 19 to 22.

<sup>5</sup> That is, unless the applicant was responsible for a breach of some obligation that did apply to the applicant. Regulation 51 says that a person does not commit an offence under the Regulations if he took all reasonable precautions and exercised all due diligence to avoid committing the offence.

<sup>6</sup> See paragraphs 15 to 18.

CTU’s staff may agree that the CTA should name that employer or the CTU as a “co-sponsor”.

15. In some cases, there is scope to specify who takes responsibility for particular trial sites. Under Part 4 of the Regulations, sponsors have to take on responsibility for putting and keeping in place arrangements to ensure the conduct of trials adheres to the conditions and principles of GCP. It is a general requirement, for the protection of people recruited into trials, that no-one may conduct a clinical trial or perform the functions of the sponsor other than in accordance with GCP.
16. This does not mean sponsors necessarily have to be answerable for all the individual arrangements related to GCP at each site in a multi-centre trial. For example, several trial networks may collaborate in a large trial. In that case, it might offer better protection if, for each network, one investigator or organisation is named as the person taking on specific responsibilities for GCP across that network. The Regulations allow the CTA to specify who is to perform the functions of the sponsor at particular sites or groups of sites. Whoever is specified will be responsible for those functions.
17. It is a general requirement that no-one may conduct a trial other than according to the protocol and the terms of the CTA, the ethics committee application and related documents. Sponsors and investigators have to take urgent safety measures<sup>7</sup> if needed. Clinicians may also take measures to protect trial subjects for whom they are responsible<sup>8</sup>.
18. In general, sponsors or specified persons may delegate tasks required to perform any of these duties. In that case, people accepting responsibility for those tasks would do so by separate agreement. The trial protocol may record this. The CTA would not name those people.
  - *The request for a CTA may allocate the sponsor’s responsibilities among several organisations*
19. As described, the Regulations allow a request for a CTA on behalf of a group of organisations or persons. If they agreed to allocate the legal responsibilities by function, there would in effect be one “co-sponsor” for each of the following sets of responsibilities:
  - a. authorisation;
  - b. GCP and conduct; and
  - c. pharmacovigilance.

Box 3 lists the Regulations related to these three sets of functions.

<b>Sponsor’s functions</b>	<b>Part</b>	<b>Regulation number</b>
Authorisation, ethics committee opinion	3	17, 18, 19, 20, 21, 22, 24, 25, 26, 27
Good Clinical Practice, conduct	4	28, 30
Pharmacovigilance	5	32, 33, 34, 35

**Box 3**

<sup>7</sup> The Directive requires sponsors and investigators to take urgent safety measures to protect against “any immediate hazard”.

<sup>8</sup> In terms of the Regulations, these people would act on behalf of a sponsor or investigator.

20. The request for a CTA will include declarations to confirm the applicant is authorised to apply on behalf of the organisation(s) or individual(s) who agree to be “co-sponsors” or joint sponsors. The MHRA requires written evidence. A request lacking these details would not be valid.
21. The ethics committee and the MHRA will expect sponsors to name someone as their contact<sup>9</sup> for regulatory communications (about inspection, for example). That single contact person would ensure the relevant “co-sponsors” and investigators are kept informed of any regulatory communications.
22. Naming a contact person for communications will not be a legal requirement. It will not affect a “co-sponsor’s” individual responsibility for ensuring action is taken if the MHRA issues a notice or request about that co-sponsor’s responsibilities under the Regulations. When urgent action is required, the MHRA will serve a notice on the “co-sponsor” responsible for taking action, copying it to the contact person.

### ***Who could take on the responsibilities of sponsorship?***

23. The remaining sections of these notes discuss issues that collaborating partners may want to consider in deciding which of them will accept responsibility for arrangements to carry out particular responsibilities under the Regulations. These sections are intended to help the partners reach agreement. They are not requirements of the Regulations. It is for sponsors to decide how to make satisfactory arrangements to comply with the Regulations.
  - *Normally, in publicly funded trials the chief investigator will act on behalf of the main research employer when submitting the request for a CTA*
24. The Directive requires that, before commencing a clinical trial, a sponsor shall submit a valid request for authorisation. In a publicly funded trial, it may be expected that the organisation or person most closely associated with initiating and managing the trial is likely to be the one named as sponsor. (If the request is on behalf of a group, the “co-sponsor” taking on the responsibilities related to authorisation is likely to be the one closest to initiation and management.)
25. Investigators initiate most publicly funded trials, and lead their management, as part of their employment. Typically, the chief investigator’s employer will be:
  - a university, or
  - a research-active provider of health care, or
  - a research funder that employs a research team directly.Sometimes, a host institution might accept the employer’s liabilities for an investigator or research team, by agreement with the primary employer and the employees.
26. Under the Regulations, the chief investigator is responsible for applying for ethical review. In publicly funded trials, the chief investigator could also be authorised to submit the request for a CTA on behalf of a sponsor (or group).

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<sup>9</sup> This person would in effect be the agent of the group taking on sponsorship responsibilities.

27. It is for the employing organisation and the chief investigator to decide whether to identify the chief investigator personally, or the organisation corporately, as the one taking on particular responsibilities under the Regulations. This depends on the extent of personal responsibility delegated to the chief investigator.
  28. In any case, by authorising someone to request a CTA, the employing organisation may also imply that it accepts responsibility for the acts or omissions of its employees in the course of the trial. The employing organisation's authority would also imply it is satisfied with the provision for indemnity or insurance. See appendix C for more on indemnity and insurance.
- *Other options*
29. The previous paragraphs describe some of the arrangements that could normally stand behind a chief investigator requesting a CTA on behalf of his/her employer. The Regulations include some flexibility and allow other approaches. The aim is to enable a wide range of high quality clinical trials to take place.
  30. The MHRA will consider valid requests from any organisations or persons that can give satisfactory assurances about the allocation of responsibilities for the initiation and management of trials. The following paragraphs describe considerations that might lead to a request for a CTA on behalf of an organisation or person that is not the chief investigator's employer.
- *The main funder may authorise the request for a CTA*
31. The main funder of a publicly funded clinical trial may be the organisation most closely concerned with its initiation as well as its financing. For example, the main funder may commission a study, or it may substantially influence the purpose and design of a proposal originally initiated by an investigator.
  32. If the chief investigator's employer is unable to take responsibility for requesting a CTA, the main funder may authorise the chief investigator to submit the request on its behalf. The main funder might do so either as a single sponsor or as the member responsible for authorisation functions among a group of "co-sponsors". Alternatively, it might authorise an agent such as a Contract Research Organisation to do so. In either case, the main funder would consider who is best placed to undertake the sponsor's responsibilities.
  33. For example, the Department of Health (DH) is willing to sponsor trials commissioned on its behalf. DH expects normally to carry out the sponsor's responsibilities through organisations that act for it under contract, such as the National Co-ordinating Centre for Health Technology Assessment. DH would also collaborate with others whenever it made sense to share out the sponsor's duties. There are at present no national arrangements under which DH (or bodies acting for DH) would take on responsibility for other trials.
  34. The MRC is also considering the circumstances when it could take on sponsorship responsibilities. A statement is on the MRC web site. Like DH, it would rely on clear understandings about local delegation of the tasks required, and would not take on liabilities that properly belong elsewhere.
  35. Many medical research charities have taken the view they could not take on any of the sponsor's responsibilities under the Regulations.

- *The health care provider responsible for the main trial site may authorise the request for a CTA*
36. Some clinical trials are conducted with healthy volunteers. Others involve NHS patients. NHS bodies have duties towards NHS patients whether or not they are recruited to trials, and some of these duties overlap with the sponsor's responsibilities under the Regulations.
  37. Not all NHS bodies have research expertise. Many have completed local research governance implementation plans. Some are equipped to consider taking on sponsorship responsibilities. From 2004, NHS bodies will report on compliance with a controls assurance standard for research governance.
  38. Within established NHS/academic partnerships that conduct trials, it is up to the partners to establish:
    - which of them is normally best equipped to accept each set of sponsorship functions under the Regulations, and
    - which of them should take the lead in requesting a CTA for a particular trial.
  39. Normally, the NHS body responsible for the main trial site would authorise the request for a CTA if it is the chief investigator's primary employer. Exceptionally, the NHS body responsible for the main trial site might agree to do so when it is not the primary employer or the main funder, if no other suitable organisation can do it.
  40. For example, a research active NHS body may have robust research governance systems. It may already be the sponsor for a programme of clinical research involving its own sites and perhaps other trial sites within a NHS Priorities and Needs R&D collaboration. The new trial may serve objectives that complement trials the NHS already undertakes.
  41. In these circumstances, the NHS body responsible for the main trial site may be willing to authorise the chief investigator to request a CTA on its behalf. Alternatively, the NHS body may authorise its R&D Director to request a CTA, or arrange for a Clinical Trials Unit to do so.
- *An individual investigator may request a CTA on his or her own behalf*
42. The EU Directive defines the sponsor as *an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial*.
  43. Sometimes, a chief investigator may request a CTA as a private individual. The request would not be on behalf of an employer. The person would be a sponsor-investigator.
  44. In that case, it would be the personal responsibility of the investigator to arrange to carry out all of the sponsor's responsibilities<sup>10</sup>, and to make arrangements for insurance or indemnity.
  45. Employers might decide not to permit employees to act as sponsor-investigator during the course of their employment, because of their potential liability as employer. NHS bodies responsible for trial sites would seek specific evidence of insurance, and require the investigator-sponsor to indemnify them.

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<sup>10</sup> Or a set of them, if the request named the sponsor-investigator together with "co-sponsors".

- *International trials*

46. It is preferable to conduct an international multi-centre trial as one trial under the same EudraCT number<sup>11</sup>. However, UK sponsors of publicly funded trials might be unwilling take on all the sponsor's responsibilities for trial sites in other countries.
47. It is best to avoid organising parallel trials, each with its own national sponsor or sponsors, because of risks to the integrity of the design. For example, that could result in sponsors in different countries making different amendments to the original protocol.
48. An alternative could be for a UK "co-sponsor" to agree an allocation of responsibilities with a UK CTU and lead organisations that have national accreditation in their own country. Between them, they could act as "co-sponsors" accepting appropriate responsibilities that cover all the trial sites.
49. Trials in several European countries require authorisation by the competent authority in each Member State concerned. The options depend on other Member States' interpretation of the scope for allocating the sponsor's duties.

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<sup>11</sup> A EudraCT number is required for each trial before a CTA request can be made to the competent authority in an EU Member State where the trial is to take place.

**Summary of responsibilities of sponsors, persons named as responsible for GCP, and investigators in a clinical trial under the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing EU Directive 2001/20/EC**

Key points

- Directive 2001/20/EC defines a sponsor as an *individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial*;
- A group can take on the roles and responsibilities of sponsorship<sup>12</sup>. See Regulation 3 for the definition of “sponsor” when it is a group.
- The parties to a group can agree in writing to allocate these roles and responsibilities to particular persons and organisations; and each party would then be responsible for the roles and responsibilities it takes on.
- Sponsors can also delegate responsibilities for which they remain ultimately responsible.
- Before initiating a trial, the sponsor should define, establish and allocate all trial-related duties and functions. The trial protocol would include a scheme of allocation and delegation.
- Appendix B shows as a diagram how the Regulations enable a group requesting a Clinical Trial Authorisation to allocate responsibilities of sponsorship in three sets: authorisation; GCP; and pharmacovigilance.

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<sup>12</sup> Among other possibilities, the investigator may take on sponsorship responsibilities

## Summary of responsibilities of sponsors, persons named as responsible for GCP, and investigators in a clinical trial under the UK Regulations implementing EU Directive 2001/20/EC

The diagram shows how the UK Regulations enable a group requesting a Clinical Trial Authorisation to allocate responsibilities of sponsorship in three sets: authorisation; GCP; and pharmacovigilance.

The UK Regulations enable allocation of sponsorship responsibilities		
<b>Sponsorship responsibilities</b> can be allocated in three sets: authorisation; GCP and conduct; and pharmacovigilance.	Clinical Trial Authorisations (CTA) can name persons (other than sponsors) <b>responsible for duties</b> relating to GCP and conduct of the trial.	These <b>investigator responsibilities</b> correspond to the sets of sponsorship responsibilities.
<b>Authorisation</b> Request CTA Permission for inspection <sup>13</sup> Notify CTA amendments Notify protocol amendments Notify end of trial		Request ethical review of the protocol
<b>GCP and conduct</b> GCP arrangements IMPs free of charge Urgent safety measures	<i>Sponsor or named persons</i>	Obtain consent  Urgent safety measures
<b>Pharmacovigilance</b> Record adverse events Record/report SUSARs Tell investigators of SUSARs Enter SUSARs on EMEA database Annual list, safety report		Report SUSARs to sponsor Report other adverse events according to protocol Supply information on deaths

<sup>13</sup> This refers to permission for inspection of premises in third countries. Under Regulation 21, if a trial is to be conducted both in the UK and at sites in other countries outside the EU where the MHRA would not normally have powers of inspection, the MHRA may ask for undertakings to permit inspection of premises.

## Agreements, insurance and indemnity

1. These notes summarise some issues that particularly affect those considering whether to authorise the use of their name on a request for a clinical trial authorisation (CTA). A more detailed note will shortly be available on potential liabilities, insurance, indemnity and risk management in clinical trials.
- *Agreements*
    2. The CTA will record a legally binding allocation of responsibilities among “co-sponsors”. The protocol will also record that particular persons or organisations have taken responsibility for key tasks required to comply with the Regulations, for example with regard to Good Clinical Practice and the protection of people recruited into the trial.
    3. Explicit agreements are good practice in research governance. However, there are no plans to make it a statutory requirement for the members a group of “co-sponsors” to have contracts between them. The need for additional written agreements or contracts may be reduced if “co-sponsors” accept responsibilities that are sufficiently defined in the Regulations and related guidelines; or which are in line with their normal legal liabilities.
    4. For example, “co-sponsors” and other relevant organisations could agree a package of indemnity and insurance arrangements (see below). They could each confirm there is indemnity or insurance for the staff or other liabilities for which they would normally be responsible under the law. They could agree which of them will arrange additional insurance for any other material risks identified during ethical review.
  - *Insurance and indemnity*
    5. Under the Directive, a clinical trial may be undertaken only if (among other things) provision has been made for insurance or indemnity<sup>14</sup>. Neither the Directive nor the Regulations specify who should make this provision. Regulation 15 makes it a responsibility of the ethics committee to consider
      - the arrangements for indemnity or compensation in the event of injury or death attributable to the trial, and
      - any insurance or indemnity to cover the liability of the investigator or sponsor.
    6. Manufacturers of medicines are normally liable for harm caused by manufacturing defects.
    7. Universities normally insure against claims for negligent harm caused by their employees. They may have insurance that takes specific account of potential liabilities arising from clinical trials.
    8. Charitable funders normally insure against claims for negligent harm caused by their employees. Some also insure against the risk of harm resulting from

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<sup>14</sup> It is one of the requirements of Article 3 of Directive 2001/20/EC that a clinical trial may be undertaken only if provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

research, if an ethics committee asks them to do so as a condition of a favourable opinion in a particular case.

9. NHS bodies and the Department of Health, like the MRC, operate within established policy for the public sector. They do not normally take commercial insurance.
10. The NHS pools the risk of claims for clinical negligence. Under NHS Indemnity for clinical negligence, NHS bodies agree to meet the cost of claims for negligent harm caused by NHS staff in the course of their NHS employment, including their involvement in clinical trials. When the NHS body owes a duty of care to the person harmed, NHS Indemnity for clinical negligence can also cover negligence by staff on contract, and others conducting research with NHS permission<sup>15</sup>.
11. NHS Indemnity does not extend to negligence for which an external sponsor is liable. It is normal for the NHS to seek an agreement with an external sponsor, documenting the liabilities that each accepts.
12. Independent practitioners providing NHS services are not covered by NHS Indemnity. They are expected to take professional liability insurance covering themselves and their staff. Their insurers may agree to cover research if the practitioner proposes it.
13. NHS Indemnity does not cover the private practice of any health professional.
14. NHS bodies, like the MRC, do not enter into arrangements under which they agree in advance to make payments to trial subjects in the event of non-negligent harm. They may consider an ex gratia payment if there is such a claim.
15. Neither the Directive nor the Regulations require no-fault compensation. It remains the ethics committee's responsibility to consider any provision for compensation in the case of harm when there is no negligence.

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<sup>15</sup> This is a summary of some of the main points in *NHS Indemnity Arrangements for clinical negligence claims in the NHS*, issued under cover of Health Service Guidance 96/48. It does not change any of the details in that guidance.