

Research and Development Forum

SPONSORSHIP PRINCIPLES

Introduction

The Research Governance Framework(s)¹ require that all health-related research has a formal sponsor. The sponsorship responsibilities for Clinical Trials of Investigational Medicinal Products (CTIMPs) are governed by the EU Clinical Trials Directive 2001/20/EC and further clarified in the Good Clinical Practice (GCP) Directive 2005/28/EC. These Directives were transposed into UK law by means of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Amendment Regulations 2006²³. These regulations will be referred to in this document as the Clinical Trials Regulations.

Under the Clinical Trials Regulations, it is an offence to conduct a CTIMP without a sponsor and the Medicines & Healthcare products Regulatory Agency (MHRA) requires evidence that a sponsor has accepted the role before a Clinical Trials Authorisation can be issued.

Basic Principles

This section outlines the principles underpinning the sponsorship of studies involving one or more institutions.

1. The sponsor is the individual or institution that takes responsibility for the initiation, management and financing (or arranging the financing) of the study. The sponsor must satisfy itself that the study meets the relevant standards and ensure that arrangements are put and kept in place for management, monitoring and reporting.
2. Sponsors can formally delegate one or more of the elements of sponsorship for example, to the chief investigator, clinical trial unit or another third party, but the sponsor remains accountable for all aspects of sponsorship whether delegated or not. The sponsor must implement procedures to ensure appropriate **oversight** of all delegated functions. This can be achieved by:
 - a) Assessing that individuals or organisations delegated sponsor functions are appropriately qualified and competent to perform those functions.
 - b) Ensuring all parties are aware of their roles and responsibilities (by clearly defining them in contracts or agreements).
 - c) Maintaining lines of communication to ensure the obligations of all parties are being met (for example by receiving progress reports).
3. The factors which determine sponsorship include: the nature of the funding body, the employer of the chief investigator and the duty of care to patients as outlined below.

¹ Country specific versions of the Framework have been published by the UK Health Departments in England, Scotland, Wales and Northern Ireland

² Medicines for Human Use (Clinical Trials) Regulations SI 2004 1031

³ Medicines for Human Use (Clinical Trials) Amendment Regulations SI 2006 1928

- a) Where a commercial organisation (such as a pharmaceutical company) funds a study for which it retains ownership of the intellectual property rights, the company invariably acts as the sponsor.
- b) Where a study is funded by a research council, medical charity or other non-commercial body, the funder may be willing to act as the sponsor, particularly where it also employs members of the research team or retains an interest in any intellectual property that is generated. It is important to note that funders do not automatically accept the role of sponsor and where this is the case, the grant application will need to confirm details of sponsorship arrangements.
- c) Where an investigator undertakes a study on behalf of his/her employing institution and the funding body is unwilling to act as the sponsor, the employing institution may act as the sponsor.
- d) Where an investigator undertakes a study in which the participants are owed a duty of care by the host rather than the investigator's employing institution, the host institution may act as the sponsor. However, the duty of care remains the responsibility of the host institution, irrespective of whether they are the sponsor.
- e) Under the Clinical Trials Regulations, it is possible for an individual investigator to take on the role of sponsor. However, many institutions prohibit their employees from doing so, in view of the potential risks this might involve.
- f) If no one is willing to take on the sponsor role, the study may not proceed.

Questions and answers relating to sponsorship of publically funded trials are detailed below.

1. What is the expectation of sponsors?

It is essential that sponsoring organisations understand their role and responsibilities and have the necessary systems and processes in place in order to support and promote high quality research. The Health Research Authority has published a document outlining its [expectations of sponsorship](#).

2. Which studies require a sponsor?

All research falling under the remit of the Secretary of State for Health must have a formal sponsor. This includes all research in health and social care that involve NHS patients, their tissue or information, staff, equipment or other resources of the NHS. There are similar requirements for research involving social care practitioners, clients and resources, where this falls under the Secretary of State for Health's remit.

3. Can there be more than one sponsor for a trial?

Where two or more organisations share a significant interest in a study, for example, one as employer of the chief investigator and another as the principal host institution, they may elect to act as **co-sponsors** or **joint sponsors**.

- **Co-sponsors** agree an allocation of defined sponsor responsibilities. The Clinical Trials Regulations group the sponsor's responsibilities by function (Part 3, 4, 5, 6 and 7) and the activities associated with these functions are detailed in Table 1. Co-sponsors divide amongst themselves both the responsibilities and the liabilities associated with sponsorship. The clinical trial authorisation (CTA) must clearly define the set of sponsorship responsibilities taken on by each party.

The allocation of sponsor responsibilities will be determined by the expertise and capacity of the individual or institution to discharge them in relation to the risk posed by the study.

- **Joint sponsors** are partner organisations who accept joint liability for all of the sponsor's responsibilities. They are jointly and severally responsible for all the duties of the sponsor, such that all are responsible in the event of a failure of any one of the partner organisations to discharge their responsibilities. Both organisations would have to have suitably qualified and trained staff to oversee all of the sponsor's activities.

N.B. Most institutions that sponsor CTIMPs have chosen to adopt sole sponsorship or co-sponsorship arrangements as they offer the greatest degree of clarity and transparency in the allocation of roles and responsibilities.

What responsibilities are undertaken by institutions sponsoring CTIMPs?

The legal responsibilities of the sponsor that are outlined in the Clinical Trials Regulations and are set out in Table 1.

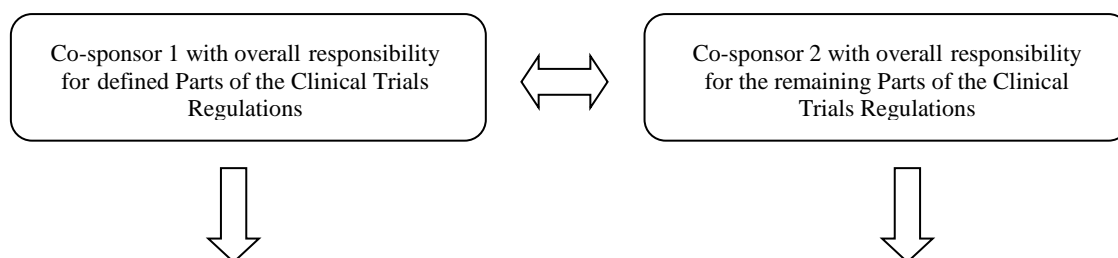
Table 1. (Reproduced with kind permission from the MHRA Guide ISBN 978 0 11 708107 9)

| Sponsor's Function and Responsibilities | UK SI 2004/1031 Reference |
|---|---|
| A. Authorisation for clinical trials and research ethics committee opinion | |
| Obtain required authorisations to commence the trial (clinical trial authorisation and favourable ethics committee opinion) | Part 3: Regs. 12, 13, 17, 18, 19 and 20 Schedules 3,4 and 5 |
| Keep records of all amendments to the authorisations and obtain approval where approvals are required | Part 3: Regs. 22, 24, 25 and 26 |
| Produce undertaking to allow inspection of premises in third countries if required | Part 3: Reg. 21 |
| Notify all relevant bodies of the conclusion or termination of the trial within the specified timeframes | Part 3: Reg. 27 |
| B. GCP and the conduct of clinical trials | |
| Ensure that the conditions and principles of Good Clinical Practice are satisfied and adhered to | Part 4, Reg. 28 Schedule 1 |
| Ensure that the trial is conducted in accordance with the protocol and subsequent amendments | Part 4: Reg. 29 |
| Notify any serious breaches of Good Clinical Practice or the protocol, or any urgent safety measures taken to the appropriate authorities | Part 4: Regs. 29A and 30 |
| Ensure investigational medicinal products and relevant devices are available to subjects free of charge | Part 4: Reg. 28 |
| Keep a trial master file to hold all documents relating to that trial | Part 4: Reg. 31A |
| Appoint named individuals responsible for archiving the trial essential documents | Part 4: Reg. 31A |
| C. Pharmacovigilance | |
| Ensure an investigator's brochure exists and is validated and updated | Part 1: Reg. 3A |

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| at least annually | |
| Keep records of all adverse events relating to that trial which are reported by investigators | Part 5: Reg. 32 |
| Record and report suspected unexpected serious adverse reactions to appropriate authorities within specified timelines | Part 5: Reg. 33 |
| Sponsor's Function and Responsibilities | UK SI 2004/1031 Reference |
| C. Pharmacovigilance Continued | |
| Ensure all suspected unexpected serious adverse reactions including those in third countries are entered into the European database | Part 5, Reg. 34 |
| Provide annual list of suspected serious adverse reactions and a safety report to the appropriate authorities | Part 5: Reg. 35 |
| D. Manufacture and labelling of investigational medicinal product | |
| Meet requirements for the authorisation to manufacture and import investigational medicinal product (including the use of hospital exemptions) | Part 6: Regs. 36 and 37 Schedules 6, 7 and 8 |
| Certification of the investigational medicinal product by a Qualified Person | Part 6: Reg. 43 |
| Two-step release process for investigational medicinal product ('technical release' and 'regulatory release') | Part 6: Reg. 43 |
| Ensure investigational medicinal product is labelled in accordance with Article 15 of Commission Directive 2003/94/EC | Part 7: Reg. 46 |

Where, for example, the co-sponsorship model is adopted, formal arrangements should be put in place:

- 1) **Between the co-sponsors** - so it is clear where all liabilities⁴ lie.
This is usually documented using a contract or a Memorandum of Understanding either issued on a trial-by-trial basis or as an overarching master agreement for all clinical trials where two or more organisations are closely connected and often collaborate (e.g. NHS Trust and university).
- 2) **Between sponsors and those delegated sponsor functions** - to ensure all parties are aware of their delegated functions.



⁴ The liabilities for fulfilling the requirements of the Clinical Trials Regulations

Sponsor functions may be delegated to third parties (either internally or externally).
Examples include: chief investigator, clinical trials unit, central laboratories and participating sites.

Diagram: An illustration where two co-sponsors allocate and delegate responsibilities and functions

4. What are the risks attached to an organisation taking on the role of sponsor?

A sponsor organisation is exposed to potential risks in a number of areas.

- Financial – e.g. claims for damages⁵ from individuals who participated in clinical trials.
- Legal – e.g. prosecution by MHRA or other regulatory authority for a breach of Clinical Trials Regulations, such as failure to comply with the conditions of ethical approval or contravention of pharmacovigilance requirements.
N.B. Clinical Trials Regulations provide a defence of due diligence ([Regulation 51 of SI 2004 1031](#)).
- Reputation – e.g. adverse publicity arising from failure of the study, failure to meet required standards of GCP identified at MHRA inspection, or from prosecution as outlined above.

A detailed risk assessment should always be performed when planning a new study and practical advice on risk assessment can be found in the [NIHR Clinical Trials Toolkit](#).

5. How can a sponsor mitigate against risk?

The following principles underpin successful risk mitigation:

- Risk assessment prior to commencement of trial and careful consideration when deciding to undertake high risk activities (the sponsor must be confident that the appropriate systems, capacity and expertise are in place and any risks are mitigated and are substantially outweighed by the benefits).

N.B. The National Institute for Health Research (NIHR) has adopted the [Research Support Services framework](#) for local health research management. Annex 5 of the support framework documents includes a planning tool which is designed to ensure operational risks are identified early and addressed proportionately.

- Ensuring that all responsibilities listed in the Research Governance Framework and for CTIMPs, the Clinical Trials Regulations have been formally assigned to and accepted by, specified institutions, groups or individuals.
- Ensuring oversight of any delegated functions (as described above).
- Ensuring the competence of the chief investigator (and the research team) and host organisation(s) to oversee, manage and conduct the study.
- Implementing appropriate training in research methods and GCP for members of the research team and for multi-site studies, ensuring site staff have the necessary training and resources to successfully conduct the study.
- Undertaking monitoring and audit of studies to detect and rectify poor compliance.

⁵ It should be noted that claims arising from clinical trials represented only a tiny proportion of the total damages figure paid out by the NHS Litigation Authority (0.002% between 1995 and 2010)

6. What are the implications for indemnity with respect to sponsorship?

A sponsor is responsible for ensuring that provision has been made for the insurance and indemnity to cover the liability of the investigator and sponsor which may arise in relation to the study.

For each study, the sponsors should check that the insurance policies that are used to provide cover contain no exclusions that could impact on the cover for research subjects. NHS indemnity arrangements provide cover for legal liabilities where the NHS has a duty of care (i.e. harm caused by negligence) and for trials run within the NHS, the sponsor must ensure that the research is covered by the NHS indemnity by confirming that NHS permission is in place for each participating site.

7. Can an institution elect to sponsor particular types of studies?

Institutions are expected to review candidate studies for sponsorship on a case-by-case basis (through a formal application/registration process initiated by the chief investigator) and should only accept the role of sponsor for studies that lie within their range of competence. For example, an organisation that has no experience or infrastructure for the management of clinical trials should avoid acting as a sponsor for such trials unless it can delegate the specific responsibilities to another organisation that has the required expertise. Similarly, an organisation lacking experience managing multi-site studies may be advised to limit itself to sponsoring single centre studies until they have developed the systems (and the competence) to expand their trial portfolio to include multi-site trials.

8. Who acts as the sponsor for Primary Care studies?

Clinical Commissioning Groups (CCGs) have the power to conduct, commission or assist the conduct of research, and the Social Care Bill creates a duty for CCGs to, “promote research and innovation and the use of research evidence.” CCGs should be engaged in supporting, enabling and coordinating others to engage in research activity. Where a CCG or practice wishes to act as Sponsor, R&D offices, which are hosted by a wide range of organisations, act as a source of advice/guidance to highlight the implications of Sponsorship and support organisations in the discharge of their duties. The R&D Forum’s Primary Care Working Group has developed a paper that outlines research support activities:

[Local support functions in primary care R&D offices following the implementation of HRA Approval](#)

Independent contractors should be discouraged from becoming sponsors of clinical trials because of the scope of responsibility involved. Where an independent contractor is considering becoming a sponsor, they should contact their professional body and their mutual indemnity society, to ensure that the appropriate safeguards for indemnity are in place. Independent contractors are not covered by NHS indemnity (for further guidance on indemnity arrangements in primary care, see [the Indemnity for GPs and other Independent Practitioners in Primary Care](#)).

9. What sponsorship arrangements are appropriate for international studies?

Guidance on international sponsorship can be found on the [HRA website](#) and the following may apply:

a) UK organisation acting as a legal representative

For CTIMPs, if the sponsor is not based in the European Economic Area (EEA)⁶, a legal representative who is established in the EEA must be appointed. The legal representative acts as the agent of the sponsor in the event of any legal proceedings instituted in the EEA (for example, for service of legal documents) but does not take on the legal liabilities of the sponsor. If a UK site is acting as a legal representative, they should ensure contracts are in place with the non-EEA sponsor so that roles and responsibilities are explicitly stated and understood.

b) A UK organisation wishing to sponsor a multi-national trial

Trials that are led by a UK coordinating centre with participating sites outside the UK. In principle, the role of sponsor can be taken by a UK organisation. Competent authority and ethics committee approval is required from each country participating and national regulations to enact the EU Clinical Trials Directive differ widely amongst countries. Not surprisingly, it is often unclear how the responsibilities of a UK sponsor align with those under other national regulations. One possible solution is for a UK organisation to take on sponsorship subject to stringent, legally-binding agreements with each of the non-UK centres and to ensure collaboration is only undertaken with centres that have a proven track record, evidence of robust quality systems and a good knowledge of their own country's regulatory requirements.

The Clinical Trials Regulations define countries outside the European Economic Area (EEA) as 'third countries'. Sponsors with sites in third countries must be aware of the additional requirements relating to such trials; for example, the requirement to enter Suspected Unexpected Serious Adverse Events (SUSARs) from third countries into the European Database.

The European Commission has published the [EU Clinical Trials Regulation](#) which will replace the EU Clinical Trials Directive. The new Regulation recognises the difficulties experienced by non-commercial sponsors conducting international trials and Article 72 sets out new provisions for co-sponsorship.

Who acts as the sponsor of student studies?

According to the Research Governance Framework, the supervisor of a student *may* act as the sponsor for research where the primary objective of the research is educational. However many institutions insist on institutional sponsorship of all their research and do not permit individual sponsorship by supervisors. The Forum does not advocate sponsorship by individuals because of the risks and liabilities involved.

Moreover, it is not always obvious whether the primary objective of a particular study is educational or is to derive new knowledge, nor is it always obvious whether an individual should be regarded as a 'student'. For example, trainees in professions such as Public Health Medicine and Clinical Psychology are required to undertake a research project as part of their training but this is often designed to generate new knowledge in addition to satisfying the training (i.e. educational) requirements.

Questions relating to specific aspects of a study may be directed to the Research Office of the organisation employing the Chief Investigator.

10. What costs will be incurred in fulfilling the role of sponsor?

All studies incur research costs which must be differentiated from other costs (see DH Guidance: [Attributing the costs of health & social care Research & Development -](#)

⁶ The European Economic Area consists of the EU countries plus Norway, Iceland and Liechtenstein.

[updated 4 May 2012](#)). Research costs include activities such as the set-up, management, monitoring, audit, and the analysis and reporting of a study.

For CTIMPs, a number of additional costs are (or may be) incurred:

- i. Fee for submitting a Clinical Trials Authorisation (CTA)
- ii. Annual service fee for maintaining a CTA
- iii. Pharmacovigilance
- iv. Costs associated with an MHRA inspection
- v. Trial Supplies (e.g. manufacture and labelling, concealment)

It is essential that all trial activities are identified early in the development process so that any associated costs can be considered during the grant application stage.

In trials sponsored by commercial companies, these costs will normally be met by the sponsor company.

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