Sponsorship Principles (Research and Development Forum)

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Introduction

The UK Policy Framework for Health and Social Care (UK Policy Framework) requires that all health-related research has a formal sponsor. The sponsorship responsibilities for Clinical Trials of Investigational Medicinal Products (CTIMPs) are regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), herein referred to as the Clinical Trials Regulations.

In the Clinical Trials Regulations, the term sponsor means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial. 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 trials 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:

    1. Assessing that individuals or organisations delegated sponsor functions are appropriately qualified and competent to perform those functions.
    2. Ensuring all parties are aware of their roles and responsibilities (by clearly defining them in contracts or agreements).
    3. 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. 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.

    1. 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.
    2. 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.
    3. 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.
    4. 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.

5. 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.

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 to support and promote high quality research. The UK Policy Framework provides more detail. The Health Research Authority has also published a Word document outlining its expectations of sponsorship.

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.

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.

  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 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 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.

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

1. Between the co-sponsors - so it is clear where all liabilities lie (The liabilities for fulfilling the requirements of the Clinical Trials Regulations).
   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.

Where two co-sponsors allocate and delegate responsibilities and functions: Co-sponsor 1 will have overall responsibility for defined parts of the Clinical Trials Regulations and Co-sponsor 2 will have overall responsibility for the remaining parts 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.

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

A sponsor organisation is exposed to potential risks in several areas.

- Financial – e.g., claims for damages (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) 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)
- 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.

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).
- Ensuring that all responsibilities listed in the UK Policy 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.

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.

Can an institution elect to sponsor only certain types of study?

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 with 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.

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.” 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 the local support functions performed by R&D offices (pdf) (.PDF).

Generally, independent contractors do not take on the role of sponsor for 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 (see the R&D Forum website Research, Indemnity and GP Practices – Advice Sheet (pdf) (.PDF)).

What requirements apply when sponsoring international studies?

CTIMPs with sites in the European Economic Area (EEA)

It is a statutory requirement for sponsors to appoint a legal representative in the UK or in a country on the approved list of European Union (EU)/European Economic Area (EEA) countries if the sponsor is not established in UK or in one of the countries on the approved list. A legal representative may:

- Act as the agent of the sponsor in the event of any legal proceedings instituted in the EEA (for example, to serve legal documents) without taking on the legal liabilities of the sponsor, or

- Enter a specific contractual arrangement to undertake some or all of the statutory duties of the sponsor, in which case the legal representative is normally regarded as a co-sponsor and would require insurance and indemnity.

From 1 January 2021:

- For trials that are conducted in the UK, the MHRA will accept the Sponsor/Legal Representative being located in the UK or in a country on the approved list of EU/EEA countries.
- For trials with a UK sponsor and site(s) in any EU Member State, a legal representative must be established in the EU.
- For trials with another third country (not member of the EU) sponsor where the legal representative was previously established in the UK, a legal representative must now be established in the EU.

The MHRA have produced guidance on the requirement for substantial amendments when changing sponsors and legal representatives. The HRA website provides further information on the requirements for a legal representative and the type of entity that may act as a legal representative.

A UK organisation wishing to sponsor a multi-national trial

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. Where it is unclear how the responsibilities of a UK sponsor align with those under other national regulations, a 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 regulation.

Who acts as the sponsor of student studies?

According to the UK Policy Framework, universities and colleges should accept the role of sponsor for all educational research conducted by their own students, unless the student is employed by a health or social care provider that prefers to take on this role.

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

All studies incur research costs which must be differentiated from other costs (see DHSC Guidance: Attributing the costs of health & social care Research & Development - 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, several additional costs are (or may be) incurred:

1. Clinical Trials Application and Amendments
2. Costs associated with an MHRA inspection
3. 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.