NuTH Sponsorship of International Studies

NJRO-REG-SOP-015

Contents

1. Background/Introduction

The UK Policy Framework for Health and Social Care Research (2017) requires that **all research** falling under the remit of the Secretary of State for Health and Social Care must have a named Sponsor. This includes research in health and social care that involves NHS patients, their tissue and/or their information. The sponsorship responsibilities for Clinical Trials of Investigational Medicinal Products (CTIMPs) are governed by the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). Under these regulations, it is an offence to conduct a CTIMP without a Sponsor and the Medicines and Healthcare products Regulatory Agency (MHRA) requires evidence that a Sponsor has accepted the role before a Clinical Trials Authorisation can be issued.

To date, the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) sponsors a wide range of studies conducted within the UK (including CTIMPs, ATIMPs and clinical investigations of non-CE marked device trials). NuTH also sponsors a limited number of international low risk (non-CTIMP) studies, however research in to rare diseases is becoming an increasingly important objective for both NuTH and its academic partners. Therefore, given that recruitment confined to the UK is often difficult and directly impacts the scientific validity of clinical trials investigating rare diseases, participation on a global scale is required.

Where NuTH agrees to sponsor a study involving international sites, NuTH is responsible, under local law, for ensuring compliance with all regulatory requirements within each participating country. However, NuTH may delegate some of its duties as sponsor to national lead sites. Nonetheless, although some sponsorship duties can be delegated, NuTH as sponsor ultimately remains responsible. Consequently, the Trust must implement sufficient processes to maintain oversight of NuTH sponsored international trials so that it can ensure all relevant legislation within each participating country is complied with and that the sponsor's legal responsibilities are met.

2. Purpose

Consequently, the purpose of this SOP is to ensure that international trials sponsored by NuTH are designed, managed and conducted in accordance with all applicable legislation, research governance and GCP requirements.

3. Scope of Document

This SOP applies to all researchers who plan to request NuTH sponsorship for an international study and all current Chief Investigators (CI) of NuTH sponsored international studies.

This SOP is also applicable to Newcastle Joint Research Office (NJRO) staff who are involved in performing sponsorship duties on behalf of NuTH, along with trial management staff and delivery teams working on NuTH sponsored, international trials.

4. Definitions

Sponsor: A sponsor is defined as an individual, company, institution, organisation or group of organisations (partnership) that takes on the overall responsibility for the initiation, management and financing (or arranging the financing) of a research project (UK Policy Framework for Health and Social Care Research, 2017; Regulation 3(1) of SI 2004/1031, Health Research Authority, 2018).

Co-Sponsorship: Where a research organisation assumes some sponsorship responsibilities in partnership with another, or a small number of other organisation(s). Co-sponsors divide amongst themselves both the responsibilities and the liabilities associated with sponsorship. In these situations it is important to clearly document the roles and responsibilities of each party. The allocation of responsibilities is determined by the expertise and capacity of the relevant individual or institution in relation to the risk posed by the study (Medical Research Council, 2018).

Joint Sponsorship: Joint sponsors are partner organisations who accept joint liability for all of the sponsor's responsibilities. They are jointly and severally responsible for all of the sponsorship duties, such that all are responsible in the event of a failure of any one of the partner organisations to discharge their responsibilities. Both organisations require suitably qualified and trained staff to oversee all of the sponsor's activities. Please note, **NuTH do not currently accept joint sponsorship**.

Legal Representative: an authorised organisation to act on behalf of the sponsor. A sponsor of a clinical trial needs to be established in the UK or country on an approved country list (which would initially include EU/EEA countries – see MHRA website for an up to date list). If this is not the case, then the sponsor must have a legal representative who is so established.

Risk Assessment: A process of identifying the potential hazards associated with a trial, and assessing the likelihood of those hazards occurring and resulting in harm.

Risk mitigation: Strategies or procedures that reduce either the impact or the probability of an adverse consequence of a hazard.

5. Roles & Responsibilities

It is the responsibility of the Chief Investigator (CI) or researcher to notify the NJRO of any potential plans to undertake an international study (this should be prior to initiating any grant applications – see section 6.1).

It is the responsibility of the CI or delegate to notify the NJRO of any potential plans to include the addition of a new international site in an existing NuTH sponsored study.

It is the responsibility of the CI/researcher or designee to provide all necessary study information and documentation to the NJRO so that a comprehensive sponsorship review can be performed by all relevant team(s) within the office.

The Regulatory Compliance Team (RCT) and/or the Research Governance Team (RGT) on behalf of NuTH as sponsor maintains the overall responsibility for the initiation, management and financing (or arranging the financing) of international research trials.

NuTH as sponsor are also responsible for ensuring that all necessary contracts are executed allowing the study to be effectively managed (this includes but is not limited to: collaboration, site, vendor and delegation of duties agreements where deemed appropriate).

For international trials involving a Clinical Trials Unit (CTU), the trial management team are responsible for fulfilling all delegated duties as listed within the 'Delegation of Sponsor Duties Agreement'.

6. Procedures

6.1 Requesting Provisional NuTH Sponsorship of an International Study

It is the responsibility of all researchers to notify the NJRO of any potential plans to undertake an international study. This notification should take place prior to initiating any grant application.

The Funding Development Team (FDT) located within the NJRO is the first point of contact for researchers wishing to develop an international study grant application (this includes CTIMP and non-CTIMP proposals).

The FDT contact details can be located on the NJRO website.

Following receipt of an initial inquiry, the FDT request the researcher to complete a Project Initiation Form (PIF). The completion of the PIF signifies the start of the process and subsequently, each grant application is given a unique identifier and is added to the agenda for the Application Assessment Meeting (AAM) for discussion (see NJRO-GEN-SOP-015: Application Assessment Meeting for further details).

At the AAM, NJRO attendees will initially identify whether the proposed research classifies as 'low' or 'high' risk. The risk classification considers all aspects of the grant application, including but not limited to; sponsorship and governance, clinical robustness and capacity, implications in supporting departments, financial considerations, contracting, compliance, lead and collaborating organisations, deadlines and funder requirements.

Consequently, given the complexities surrounding international trials (e.g. bespoke contracting, alternative legislation, cost negotiation, private insurance cover and indemnity etc.), this will somewhat increase the risk rating.

The assigned risk rating determines the next steps within the funding application process – therefore please see the NJRO-GEN-SOP-015: Application Assessment Meeting SOP for further details.

It must be noted that the Trust is not obliged to automatically sponsor any research and the NJRO, RCT or applicable committees may reject proposals for a variety of reasons as documented in the NuTH 'Research Sponsorship Policy' (NJRO-GEN-POL-002).

The Trust also maintains the right to terminate sponsorship if deemed necessary.

During the funding application process (as per NJRO-GEN-SOP-015: Application Assessment Meeting), the additional costs of including international participating sites must be taken in to consideration (e.g. some of these may include the costs of competent authority and ethics committee reviews per country; costs of translation services; insurance costs; monitoring activities etc.). The FDT will liaise with all relevant stakeholders, including sponsor, to identify these costs.

6.2 Risk Assessment

For all NuTH sponsored high risk studies falling under the RCT, a comprehensive risk assessment should be undertaken at protocol development stage so that any potential

hazards associated with the trial can be identified and an assessment can be made regarding the likelihood of those hazards occurring and resulting in harm.

The studies usually falling under the RCT which require comprehensive risk assessments include all NuTH sponsored:

- CTIMPs
- ATIMPs
- Clinical Investigations of Non-CE Marked Devices
- Randomised surgical intervention trials
- International, multicentre studies

The risk assessment should preferably be performed at an early stage of protocol development so that any required modifications to mitigate hazards can be incorporated in to the trial.

The risk assessment should be completed using the 'Clinical Trial Risk Assessment Form' (CTRAF) (Parts A & B) as documented within NJRO-REG-SOP-004.

Prior written confirmation from the RCT must be sought if any alternative risk assessment template is to be used (a copy of the template should be submitted to: tnu-tr.sponsormanagement@nhs.net).

The CI and trial management team are responsible for populating the CTRAF (or alternative template) and submitting this to the RCT via the sponsor management inbox (tnu-tr.sponsormanagement@nhs.net) for sponsor review/comments.

Once all comments have been addressed, the CTRAF (or alternative template) must be finalised and signed off by the sponsor, CI and trial management team prior to protocol sign off or final submission of the trial documentation to the appropriate Research Ethics Committee (REC) and Competent Authority (if applicable) within each member state.

The risk assessment also represents a 'living' document that should be reviewed and updated throughout the life cycle of the trial. This reflects the nature of potential risks/hazards which may differ in response to trial proceedings (see NJRO-REG-SOP-004).

If it is determined that an update to the risk assessment is required, the CI and trial management team are responsible for updating the risk assessment and submitting any updates to Sponsor for review. As mentioned previously, the updated risk assessment must be finalised and signed off by the sponsor, CI and trial management team.

For further information on the risk assessment Process including completion of the CTRAF (or alternative template), please refer to NJRO-REG-SOP-004.

Please note: due to the complexities associated with international trials, the CTRAF (or alternative template) may be amended on a trial by trial basis so that additional risks can be considered and appropriate mitigation strategies put in place.

Examples of common risk areas that must be considered for international trials include, but are not limited to: variations in legislation/local policies/procedures/standard of care; insurance and indemnity cover; changes in the political environment; data sharing/transfer across territories; transfer of human tissue; translation requirements; oversight of sites across a wide geographical area etc.

6.3 Feasibility and Selection of International Sites

As part of the risk assessment, the risks associated with international and UK based sites are considered.

It is often unclear how the responsibilities of a UK sponsor align with those under other national regulations. As such, NuTH may only take on the sponsorship of an international study subject to stringent, legally binding agreements with each of the non-UK centres.

Although site identification and selection is often a task delegated to the CI via the Delegation of Sponsor Duties Agreement, it is important that collaboration is only undertaken with centres that can demonstrate sufficient understanding of (and compliance with) their own country's requirements and have the appropriate experience and resource to carry out the study.

Consequently, feasibility documents for all proposed international centres must be submitted to the RCT via the sponsor management inbox (tnu-tr.sponsormanagement@nhs.net) so that sponsor can assess whether all required sponsorship and legislative requirements can be fulfilled within each country.

Information to be considered within feasibility requests to international sites may include (but are not limited to):

- **Relevant contact details** (e.g. Principal Investigator (PI), lead research nurse/ coordinator, R&D team, contracts team, relevant support departments, the Patient Liaison Service and the competent authority/ethics board).
- **Information regarding site resources** (e.g. research personnel, clinical resources & equipment, web based electronic systems, IT access for monitors, fluency in spoken and written English, translation services etc.).

- **Local regulatory & ethics processes** (including requirements around medical registration, study set up, clinical trials authorisation, competent authority & ethics review, timelines from submission to approval, documentation required for study set up, ionising radiation regulations, amendment process, costs associated with study set up and approvals).
- **Safety reporting** (including emergency out of hours process, adverse event reporting requirements for each nation including timelines/processes/documents, personnel responsible for safety reporting, annual reporting requirements, translation of reports, transmission of safety information to Sponsor).
- **Insurance and indemnity requirements** (including local regulations and expectations; costs associated with this; variability between countries etc.)
- **Archiving** (including details of any dedicated archiving facility, archiving policies, timelines, costs etc.).
- **Protocol & Study Design** (number of eligible patients, standard of care in patient population, cost accountability for standard care procedures, recruitment projections, patient identification methods, use of Participant Identification Centres (PICs), competing studies, protocol compliance).
- **Data collection** (experience with electronic data entry, accessibility of electronic web based databases, IT systems currently in use)
- **Samples** (regulatory requirements and local requirements for sample storage, transfer & analysis; contractual requirements including Material Transfer Agreements).
- **Laboratories** (local laboratories to be used; accreditation status; ability to conduct required tests; associated quality management systems; staff training; storage facilities; contingency plans).
- **Pharmacy requirements** (availability of IMP; clinical trial services; staff qualifications/experience/training; GCP training; Pharmacy SOPs; IMP storage facilities; QP certification; labelling; audit documentation including prescription & accountability records)
- **Social Media** (related policies; site presence on social media; approval processes for posting information)

If a proposed international site provides insufficient detail in their responses to the feasibility assessment, NuTH as Sponsor retains the right to deny site involvement within the study.

Furthermore, NuTH may also deny involvement of particular countries on the grounds of risk, safety, integrity and politics.

When considering the involvement of third countries (i.e. countries outside the European Economic Area), it is also important to consider any additional requirements relating to such trials, such as the requirement to enter all Suspected Unexpected Serious Adverse Reactions (SUSARs) from third countries in to the European database (R&D forum, 2016). Such requirements should be obtained as part of the feasibility assessment.

The information gathered from the feasibility questionnaires should be used to plan study/country set up.

6.4 Insurance and Indemnity

Insurance and indemnity arrangements also remain a standard item within the risk assessment and feasibility assessments as it important to ensure that appropriate arrangements are in place when setting up international studies.

In accordance with SI 2004/1031 (Part 2 (14) Schedule 1), the following condition applies to all clinical trials:

> 'Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial'.

The RCT are 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 any NuTH sponsored, international clinical trial.

NuTH provides standard NHS indemnity to cover for legal liabilities where the NHS has a duty of care (i.e. harm because of negligence by its employees). For trials run within the NHS, NuTH as Sponsor are also responsible for ensuring that the research is covered by the NHS indemnity by seeking confirmation that NHS permission is in place for each participating site (R&D Forum, 2016).

However, given that NHS indemnity applies to UK centres only, alternative insurance arrangements must be implemented for international centres that align with each country's local regulatory requirements. This information will be sought and confirmed when conducting site feasibility assessments.

As a result, insurance and indemnity for international studies will be arranged on a study by study (and if necessary, site by site) basis via NuTH and their official brokers. The cost for international insurance will not be covered by The Newcastle upon Tyne Hospitals NHS Foundation Trust.

All relevant insurance policies that are used to provide cover should be checked by the sponsor and CI to ensure that they contain no exclusions that could impact the cover for research subjects. If required, legal advice may be sought.

Furthermore, maintenance of insurance cover includes (but is not limited to) ensuring that renewal arrangements are in place to avoid cover lapsing; ensuring the insurance provider is informed of amendments where applicable; and maintaining a valid insurance policy and certificate of insurance.

6.5 Delegation of Sponsor Duties

Sponsors can formally delegate one or more of the elements of sponsorship to the CI, CTU or another third party, however the sponsor remains accountable for all aspects of sponsorship whether delegated or not.

Consequently, for NuTH sponsored international trials, procedures should be put in place to ensure appropriate oversite of all delegated functions. Ways in which this can be achieved include:

- Assessments to ensure that all individuals/organisations delegated sponsor functions are appropriately qualified and competent to perform those functions. This may include the review of CVs and GCP certificates or via conducting vendor assessments on all relevant third parties (see NJRO-REG-SOP-014: 'Vendors Management' SOP for further details).
- Confirmation that all parties are aware of their roles and responsibilities. These can be set out clearly within a sponsor 'Delegation of Duties Agreement' or where vendors are included as a third party, via a Technical Agreement.
- Maintenance of regular communication lines to ensure obligations of all parties are being met. This may include, but not limited to:
    - Sponsor attendance at Trial Management Group (TMG) meetings and/or sponsor review of meeting minutes
    - Submission of reports to sponsor for review (e.g. annual progress reports; development safety update reports; funder reports, monitoring reports, deviation/violation reports; Serious Adverse Event reports etc.)
    - Inclusion of Sponsor in all relevant email correspondence
- Completion of audits (where required) to ensure that any delegated duties are being fulfilled.

Where international sites are expected to perform certain duties on behalf of sponsor, a 'Delegation of Sponsor Duties Agreement' should be put in place between NuTH (sponsor) and each non-UK site. Examples of sponsor duties that may be delegated to non-UK sites

are listed below, however these should be determined on a study by study, and site by site basis:

- Submission and tracking of study application to local ethics committee & competent authority;
- Obtain any additional, local approvals as required;
- Submission and tracking of amendments to local ethics committee and competent authority;
- Submission of urgent safety measures or expedited safety reports to the relevant REC and competent authority;
- Submission of annual reports to the REC and competent authority; and
- Submission of final study report to the local REC and competent authority.

All duties to be delegated should be listed within the 'Delegation of Duties Agreement' so that it is clear to the research site (or alternative party) which functions they are required to perform. The delegation of duties should also comply with local legislative requirements.

The Delegation of Duties Agreement should then be signed by all relevant parties to document that this has been agreed and accepted by sponsor and each delegate.

When a legal Representative is required, a formal delegation of duties contract will be in place between organisations. Such contracts may be bespoke and will be assessed on a case-by-case basis.

Where by a delegated party outsources duties to a third party (for example, a Clinical Research Organisation), it is the delegated parties responsibility to fully vendor assess the third party and ensure appropriate contracting. Sponsor will require a copy of the assessment and contract to ensure oversight and retain the right to audit third parties as appropriate.

6.6 Contracting and Agreements

NuTH may only take on the sponsorship of an international study subject to stringent, legally binding agreements with each of the non-UK centres. These are likely to be bespoke agreements depending upon the nature of the study and the sites involved.

The Grants and Contracts Team within the NJRO will lead on the preparation and negotiation of the required agreements.

Legal advice/input may be sought where required.

6.7 Regulatory Considerations

Competent authority (where applicable) and ethics committee approval is required from all participating centres within each country. However it is important to note that national regulations to enact the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) can differ widely amongst countries.

The European Commission has published the EU Clinical Trials Regulations which recognises the difficulties experienced by non-commercial sponsors conducting international trials and Article 72 sets out new provisions for co-sponsorship where applicable (R&D Forum, 2016).

NuTH may, on occasion, consider co-sponsorship, however a comprehensive risk assessment would be required along with an agreement ensuring clear and effective division of duties. The Trust however does not accept joint sponsorship.

In studies that include vulnerable populations, such as children/young people and adults lacking capacity, local governing legislation must be taken in to account. Furthermore, for paediatric research, the legal age of children and reporting requirements differ in each country therefore this should be taken in to consideration when planning data cleaning and reporting activities.

Furthermore, the difference in definition of personal data and its governing legislation in different countries must be considered in the protocol design.

6.8 Translation of Study Documents

Within international studies, there may be the requirement to translate study documentation (including patient facing documents, protocols, study manuals etc.) in to native languages depending upon the countries involved and their local requirements.

The ICH GCP Addendum E6(R2) confirms that the language used within oral and written information about the trial, including the written informed consent form, should be understandable to the subject.

Thus, in order to ensure the accurate translation of study documents, a reputable translation company should be used as confirmed by an appropriate vendor assessment (or equivalent review) performed by the RCT as sponsor (see NJRO-REG-SOP-014: 'Vendors Management' SOP). A vendor assessment (or equivalent review) should be performed in order to ensure that the translation services are provided by appropriately trained, qualified and certified personnel. As part of the vendor assessment process for translation service providers, the appropriate ISO certification must be confirmed.

Non-Disclosure Agreements may be put in place with translation service providers where deemed necessary; however clauses around confidentiality may alternatively be covered in relevant contracts with the vendor.

When translating documents in to native languages, the use of 'back translation' should be incorporated in order to ensure that all documents have been translated correctly and accurately as deemed appropriate.

QC checks of the translated documents should also be incorporated where necessary in order to confirm their accuracy; this should include checks of correct version control.

Where appropriate, it is also important to ensure that all amended documents are translated accordingly as per local requirements.

6.9 Green Light Process

No research activity shall commence at international sites until sponsor green light has been received.

Please refer to NJRO-REG-SOP-005: 'Regulatory Green Light Process for NuTH sponsored high risk studies' for further details regarding this process.

6.10 Addition of International sites to an existing trial

For existing NuTH sponsored studies, if a CI wishes to add any international sites via an amendment, this must be discussed with the sponsor team and sponsor approval must be sought before contact is made with sites.

Please refer to NJRO-GEN-SOP-017: addition of sites for further information.

7. References

UK Policy Framework for Health and Social Care Research (2017)

Medicines for Human Use (clinical Trials) Regulations 2004 and the Amended Regulations 2006.

Medicines and Healthcare products Regulatory Agency (MHRA) Good Clinical Practice Guide (2012).

Research and Development Forum (2016) Sponsorship Principles. Website: http://www.ct-toolkit.ac.uk/routemap/sponsorship/downloads/sponsorship_principles_V5Jun16.pdf [Accessed 31st July 2018].

Medical Research Council (2018) Sponsorship and Indemnity. Website: https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/sponsorship-indemnity/ [Accessed 31st July 2018].

NJRO-GEN-POL-002: Sponsorship Policy

8. Appendices

N/A