York Foundation Trust R&D Unit
SOP
R&D/S83

Application for Sponsorship of a Non-CE Marked Medical Device Study

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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This SOP will normally be reviewed at least every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	24th August 2017	
2.0	15th July 2019	Change of author. Change of link to R&D website. Updating of SOPs titles. Incorporation of Organisation Information Document. Removal of specific submission instructions to MHRA – referral to website for up to date details.

Contents

1 Introduction, Background and Purpose

The Sponsor is the organisation that takes on responsibility for confirming there are appropriate arrangements to initiate, manage and monitor, and finance a study. For any research that takes place in the context of the NHS or Social Care services, it is a requirement that a Sponsor is identified.

The Sponsor has the responsibility for ensuring that all the necessary arrangements are in place before the study can proceed, including:

- ensuring that the research study has obtained scientific quality approval from the necessary bodies;
- ensuring that the study has obtained ethical approval where required;
- ensuring arrangements are in place for the monitoring and reporting of research;
- ensuring the research team have access to resources and support to deliver the research as proposed.

When an organisation agrees to sponsor a research study it takes on a major responsibility. It is important to identify a sponsor as early as possible and, in fact, many funding bodies require a sponsor to be agreed in principle prior to accepting a funding application.

2 Who Should Use This SOP

This SOP is relevant to researchers seeking sponsorship by the Trust of a research study that is a non-CE marked Medical Device study.

For clarity: This SOP applies to clinical investigations of non-CE-marked medical devices undertaken for CE marking purposes. Such investigations are subject both to regulation by the MHRA as the Competent Authority (under the Medical Devices Regulations 2002) and to ethical review by NHS RECs.

For other research studies that are undertaken in the NHS involving CE marked medical devices used for their intended purpose without modification, investigators should refer to R&D/S82 (Application to the Trust for Sponsorship of a Research Study).

Please see Appendix for Question and Answer information for Medical Device Studies giving examples of the different approvals that may be required for different types of medical device study.

3 When this SOP Should be Used

This procedure applies ONLY when an investigator seeks sponsorship by the Trust for a research study using a non-CE marked device. This SOP should not be used when applying for sponsorship of a CTIMP study or for device studies where a notice of no objection is not required from the MHRA. The procedures for applying for sponsorship for other types of study are covered on other SOPS (refer to Section 5). If you are unsure as to which SOPs apply to your application for sponsorship, seek early advice from the R&D Unit.

4 Procedure(s)

This SOP makes reference to information contained on the Health Research Authority (HRA) web pages. This information is not reproduced here but readers are advised to refer directly to the HRA website for the most up to date information and advice. http://www.hra.nhs.uk/

4.1 Contacting the R&D Unit

It is important to contact the R&D Unit at this early stage if you have not already done so. The exact procedure for applying for Sponsorship will vary depending on the nature of the study and therefore it is essential to seek early advice if in any doubt. Regardless of the process, a written protocol is always required (see section 4.2).Where the regulatory process may not be clear advice should be sought from the MHRA by email. Writing the Protocol is always required (see section 4.2).

Where the regulatory process may not be clear advice should be sought from the MHRA by email.

4.2 Writing the Protocol

Investigators who are still at the "ideas" stage, may contact the R&D Unit's Research Adviser for assistance. Guidance for writing a protocol and a suitable protocol template are available via the R&D Unit's website. It should be noted that the protocol template is designed to be applicable to all studies and should be edited to omit those sections that are not relevant to the study being developed.

One of the R&D Unit's Research Advisors will advise you of any additional documents that are required in addition to your protocol at this stage; for example a consent form, patient information sheet or a data collection sheet. The documents that will be required will vary depending on the nature of your project.

The Unit's Research Adviser can offer advice about research questions, the protocol or associated documents. Refer to R&D/G05 for further guidance.

4.3 Sourcing Funding

As the Sponsor is responsible for determining whether the study is appropriately resourced it is important that the true costs of the research study are assessed at an early stage and appropriate funding secured. A research study sponsored by the Trust should not have an unacceptable financial cost to the Organisation.

If external competitively awarded funding for the study has already been sourced then submit the protocol and supporting documents (including funding award letter and copies of peer reviews) to the R&D Unit as described in section 4.5.

If there is no funding to support the study then this must be made clear in the application.

4.4 The Sponsorship Review Process

The R&D Unit offers a proportionate review process for some Sponsorship applications, however this is not applicable for any medical device studies.

Sponsorship applications are expected to be carefully considered and must be supplied with a full suite of documentation that would be suitable for submission to the Health Research Authority (HRA) and Medicines and Healthcare Products Regulatory Agency (MHRA). Applications for Sponsorship from the Trust will only be processed for consideration by the R&D Unit when complete so applicants are advised to supply the correct documentation to avoid unnecessary delay (see Section 4.5).

4.5 Submitting the Application to the R&D Unit

Investigators should email a complete set of application documents to the R&D Unit at research.governance@york.nhs.uk. This should include:

- Study protocol (dated and version controlled);
- Patient Information Sheet (where applicable) following HRA guidance;
- Consent Form (where applicable) following HRA guidance;
- Case Record File (where applicable);
- CVs for Chief Investigator (CI) or Principal Investigator (PI) and all other investigators in the team – use HRA guidance for this;
- Drafts of any other communication with patients, participants, GPs or recruitment advertisements – use HRA guidance;
- Any relevant draft contracts or confidentiality agreements that investigators have received from other parties;
- Any completed declarations of conflict of interest (see R&D/G06);
- Study risk assessment (see R&D/F15);

All documents should be version controlled and dated on each page (preferably in the header or footer).

In addition, the Investigator must provide written confirmation that the device manufacturer is prepared to make the necessary regulatory submission to the MHRA and that funding for this submission is available.

The application must be made to the R&D Unit by the Chief Investigator (CI) or Principal Investigator (PI).

4.6 Sponsorship review of application

The Research Adviser will organise the external and internal reviews required before the application is submitted to the Trust's R&D Group for a Sponsorship decision. Reviews may include, but are not limited to:

- Peer review
- Statistical review
- Pharmacy review (where applicable)
- Laboratory review (where applicable)
- Financial review by the R&D Unit
- Any other support department review (where applicable)
- Research QA Manager review and a monitoring plan developed

Once received, copies of the reviews will be sent to the CI/PI as soon as possible. The aim is to do this within 4 weeks but investigators will appreciate that we can only request external reviewers to meet our deadlines and they may be unable to do so. The CI/PI will have the opportunity to respond to the

reviewers' comments. Once a response from the CI/PI has been received or confirmation of no response is given, the complete application will be booked into the next available slot at an R&D Group meeting.

The R&D Group will consider the complete application and make a decision as to whether the Trust is able to act as sponsor for the trial. The CI/PI will be invited to attend the relevant part of the meeting. The Group's decision will be communicated to the CI/PI in writing usually within 10 working days.

The agreement of the Trust to act as sponsor for a research study will allow the applicant to proceed with identifying other Sites (where applicable), putting in place other practical arrangements, and proceeding with applications for an ethical opinion (where required), any other regulatory bodies and HRA approval.

4.7 Completing the IRAS application

Before making regulatory submissions the investigator must incorporate all protocol and related document amendments, as specified during the sponsor review process.

Once any requested changes have been incorporated the investigator can use the Integrated Research Application System (IRAS) to complete the necessary application forms. The IRAS system can be used to make applications all the approvals required (e.g. REC, MHRA, HRA).

Advice on setting up an IRAS account or completing the form can be obtained from the R&D Unit's Research Adviser. It is ESSENTIAL to consider very carefully the filter questions on the first page of the form as the responses to these will amend the form content so that it is appropriate for the application being submitted. If in any doubt, investigators should contact the Research Adviser for advice to avoid spending time completing sections of the form that are not applicable to their study or to omit sections that would be required and will subsequently invalidate the application.

Careful consideration should be given to the Medical Device questions on the filter page as a failure to answer these correctly may result in an investigation being undertaken without the correct approvals in place.

Once completed, the IRAS form should be transferred to the Research Adviser for review and electronic authorisation on behalf of the Sponsor. Submission to the relevant external bodies can then be made following the instructions on the HRA and MHRA website.

4.1.1 <u>MHRA notice of no objection submission</u>

Please refer to the relevant pages of the MHRA website for details on the required format of this information and the submission requirements.

4.1.2 REC/HRA submission

For multisite studies the investigator should complete a Organisation Information Document (OID) and Schedule of Events (SoE) or SoECAT as the OIDwill form the site agreement between sponsor and participating organisations. The completed documents must be reviewed and approved by the R&D Unit prior to being submitted to the HRA along with the IRAS application. Templates and further information can be found on the HRA website.

The applicant should liaise with the REC (where appropriate), any other regulatory bodies, and the HRA to respond to any queries and submit further information as required.

4.8 Application to commence at Sites (capacity and capability)

Once approval has been received in writing from the REC and HRA and a notice of no objection issued by the MHRA, then the final approved set of documents must be submitted to any NHS Organisation that is to be a study site (including York Teaching Hospital NHS Foundation Trust (refer to S14). The documentation that should be included in the local information pack to participating sites is detailed on the HRA website. For multisite studies the application pack must be submitted to and reviewed by York Teaching Hospital before being sent to other Sites.

Following receipt of the application documents, the R&D Unit will review the documentation and make any insurance, contract or similar arrangements that are required.

Where appropriate a suitably qualified Medical Expert will be appointed for the study and any study oversight committees established and terms of reference agreed.

Site Initiation and appropriate study/SOP training should be undertaken as instructed by the Sponsor and documented.

At the end of the setup process, and once all arrangements are in place, confirmation of capacity and capability will be issued along with permission to begin recruitment.

If, however, the R&D Unit considers that significant changes have been made to the study as a result of the regulatory applications, it may be necessary to return the study to the R&D Group for further consideration as to whether the proposed changes affect sponsorship of the study.

Note that any change to the approved study documentation or study management after confirmation of capacity and capability has been issued will constitute an amendment to the study. All amendments must be processed following the R&D Unit's SOPs (refer to Section 5).

4.9 Important points to remember regarding fees and amendments

All applications and amendments submitted to the MHRA require a fee to be paid. Please liaise with the R&D Unit to ensure this is done.

It is essential to consider any changes made to the study documentation during the application process and to consider whether this would require an amendment to be submitted to any other bodies.

Once an investigator has received a letter of no objection from the MHRA and approval from REC/HRA, it is a requirement to notify these bodies of proposed changes to the investigation. Important information regarding how to do this is available on the HRA and MHRA websites.

For device studies, a further letter of no objection must be received from the MHRA before the proposed changes are implemented.

Such amendments requiring notification to MHRA would include changes to:

- the device under investigation
- study documentation, including the clinical investigation plan
- investigators or investigating institutions
- changes requested by an ethics committee

5 Related SOPs and Documents

R&D/S02	Application to the Trust for Sponsorship of a CTIMP
R&D/S14	Issuing Confirmation of Capacity & Capability
R&D/S74	Making Amendments to Trust Sponsored Research Studies
R&D/S82	Application to the Trust for Sponsorship of a Research Study
R&D/G05	R&D Unit Research Adviser Services
R&D/G06	Conflicts of Interest in Research
R&D/F15	Risk Assessment Form

http://www.hra.nhs.uk/

https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

6 Questions and Answers – Medical Devices

QUESTION: I am a researcher at a healthcare establishment at a very early stage in my development and looking at proof-of-concept before I take the development any further. What approvals do I need?

Products manufactured in-house in a health care establishment and undergoing testing for proof-of-concept are not subject to the provisions of the Medical Devices Regulations provided that the device is being manufactured and used on patients within the sole legal entity.

In circumstances where the in-house manufacturer sees and intends a commercial medical application in the results generated (irrespective of whether the manufacturer and subjects are part of the same legal entity) the manufacturer will need to notify the MHRA of a proposed clinical investigation. If there is any doubt as to the interpretation, please contact the MHRA.

Ethical review is not required for a proof-of-concept study provided that:

- *assignment of patients to a particular therapeutic strategy or diagnostic procedure is not decided in advance by a protocol, but falls within current clinical practice;*
- *the decision to use the product is clearly separated from the decision to include the patient in the study;*
- *no diagnostic or monitoring procedures will be undertaken other than those ordinarily applied in clinical practice.*

QUESTION: I am employed by a medical device manufacturer and we are at a very early stage in our development and looking at proof-of-concept with a clinician before we take the development any further. What approvals do we need?

Manufacturers wanting to do a proof-of-concept study need both REC and MHRA approvals for a proposed clinical investigation.

QUESTION: Do I need to obtain regulatory approval from the MHRA if I intend to use a CE-marked device for its intended purpose?

For a study involving a CE-marked device being used for its intended purpose, the sponsor does not need prior regulatory approval from the MHRA (which is the UK competent authority both for medicines and devices).

QUESTION: Do I need to obtain regulatory approval from the MHRA if I intend to use a non-CE-marked device?

For a clinical investigation involving a non-CE-marked medical device (i.e. a new or substantially modified device, or an existing device with a new function, feature or material), or a CE-marked device being used for a new intended purpose, the sponsor is likely to require a Notice of No Objection from the MHRA prior to commencing a study.

There are certain circumstances where use of a non-CE-marked device used within a healthcare establishment may not be covered by the provisions of the Medical Devices Regulations/Directives. Further advice on this can be found on the MHRA website.

QUESTION: Can you summarise the sorts of studies which are defined as 'non-interventional studies' that do not require ethical review?

If all the following criteria apply, the study does not require ethical review:

- *study of a CE-marked product being used within its intended purpose;*
- *assignment of patients to a particular therapeutic strategy or diagnostic procedure is not decided in advance by a protocol, but falls within current clinical practice;*
- *the decision to use the product is clearly separated from the decision to include the patient in the study;*
- *no diagnostic or monitoring procedures will be undertaken other than those ordinarily applied in clinical practice;*
- *epidemiological methods are used for the analysis of data.*

The above are broad criteria. There will always be borderline areas. For further information and examples on whether ethical approval is required, see the Appendix to Approval of medical devices research (version 2 April 2008).

QUESTION: The proposed study is a post-marketing study. Will it require ethical approval?

Post-marketing studies are generally classified as service evaluations and do not require REC review. However, REC review is generally required for:

- *Any randomised controlled trial*
- *A case series study involving additional research procedures, e.g. additional blood samples or imaging, outside those normally employed in the routine clinical management of the patient*

If required by journal as a condition of publication, the REC may be willing to review the study. However, the editor of the journal will usually accept a letter from the REC chair or NRES confirming ethical review is not required.

QUESTION: My study is a dual clinical trial of an investigational medicinal product (CTIMP)/medical device. What regulatory approvals do I require?

If the medical device is CE-marked and being used for its intended purpose it is classified only as a clinical trial of an investigational medicinal product (CTIMP), as for review purposes the device is not the object of the trial. Several scenarios are described on the MHRA website. If in any doubt, please contact the MHRA. If the trial requires approvals from the MHRA, both as a CTIMP and a medical device, the filter in the Integrated Research Application System (IRAS) will create both types of application with all the relevant sections included.

QUESTION: Do I have to use a flagged committee for my research involving medical devices?

Booking medical device studies through the Central Allocation System (CAS) is strongly recommended so they can be allocated to a flagged REC with experience of reviewing such research. However, applicants have the discretion to book the study direct with a REC in their locality if preferred. Dual clinical trial of an investigational medicinal product (CTIMP)/medical device studies must go to a REC recognised by the United Kingdom Ethics Committee Authority (UKECA) to review CTIMPs or a dual flagged CTIMP/medical device REC via CAS.

QUESTION: I am expecting my device to be granted a CE-mark very soon. Do I have to wait until I it is granted before I submit my application?

An application to the MHRA will not be required if the device will be CE-marked before it is supplied for use in the clinical investigation. However, where the device will not be CE-marked when the study commences, an application to the MHRA should be made. The REC application may be made prior to the CE-marking on the understanding that the study will not begin until the CE-mark is obtained. The REC will require evidence of this as a condition of its favourable opinion.

QUESTION: Do I have to wait for the results of the MHRA review before I submit my application to a REC?

The application for MHRA review of the clinical investigation may be made either in parallel or in sequence with the application for the ethical opinion. It is not essential to have the Notice of No Objection in order to make a valid application to the REC or to obtain a favourable ethical opinion. The REC should be provided with a copy of the Notice of No Objection when available, either in the course of the ethical review or following the issue of a favourable opinion.

QUESTION: What if I make my application in parallel and the MHRA requires significant changes?

Where a favourable opinion is given before a Notice of No Objection is issued, and the sponsor has agreed amendments to the study with the MHRA that require significant changes to be made to the terms of the REC application or the supporting documentation, a notice of amendment form should be submitted to the REC for review.

QUESTION: What if I make my application in parallel and the REC requires significant changes?

The MHRA requires notification of all changes. It is the responsibility of the sponsor to ensure that the MHRA (Devices) is informed.

QUESTION: Can you clarify the different roles of the MHRA and NRES in their review of a manufacturer-led clinical investigation?

The MHRA addresses the safety and performance of the device while the REC considers ethical issues. The MHRA will make an assessment of the documentation which will include the protocol, and the following where relevant:

- device detail and design

- materials
- toxicology and biological safety
- sterilisation validation
- electrical safety
- safety and usefulness of medicinal substance
- safety and appropriateness of use of tissues of animal origin.

RECs are not scientific committees, though they need to be able to understand the purpose and methodology of the research. Occasionally the REC will seek further information from the MHRA in order to make an ethical decision on the study (e.g. the assessment of risk which the MHRA has carried out as part of its review). The MHRA is under a duty of confidentiality and will seek the permission of the manufacturer before disclosing any information to the REC. Further guidance on communications between the MHRA and REC can be found in Communications on medical devices investigations (version1 April 2008).