Standard Operating Procedure

GAINING AND MAINTAINING RESEARCH AUTHORISATIONS including sponsor, HRA and MHRA

SETTING Trustwide for research conducted within UHBristol and/or sponsored by UHBristol

AUDIENCE All staff involved in setting up and conducting research

ISSUE
- Relevant to Clinical Trials of Investigational Medicinal Products
- Applying for sponsorship, HRA, MHRA and other authorisations.
- Submitting reports, notifications and updates to maintain authorisations.

Standard Operating Procedure (SOP)

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Approved by:	Trust Research Group		
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Date Reviewed	Version number	Version Date	Effective Date	Reason for change	Author/Responsible person	Authorised by
Original Policy	1.0	27/07/2015	17/08/2015	New SOP	[redacted]	[redacted]
19/08/2015	1.1	19/08/2015	14/09/2015	Minor changes to incorporate consultation feedback	[redacted]	[redacted]
02/12/2015	1.2	02/12/2015	23/12/2015	Minor updates to wording	[redacted]	[redacted]
November 2016	1.3	05/12/2016	16/02/2017	Annual review undertaken. Minor updates made, removed duplication and signposted to other R&I SOPs where applicable.	[redacted]	[redacted]

1. Purpose

The purpose of this document is to signpost researchers to relevant resources to gain and maintain the authorisations for conducting research sponsored and/or hosted by University Hospitals Bristol.

2. Scope (areas/people in and out of scope should be defined)

In scope: research hosted by, and/or sponsored by UHBristol.

Out of scope: Audit and service evaluation/development. Audits must be reviewed by the UH Bristol Clinical Audit Department. Non-research studies involving questionnaires and surveys should be reviewed by the UHBristol Questionnaire, Interview and Survey Group (QIS).

3. Definitions/Abbreviations

ARSAC	Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
HEI	Higher Education Institute
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
R&I	Research & Innovation
RMO	Research Management Office
SOP	Standard Operating Procedure
UHBristol	University Hospitals Bristol

4. Procedure

4.1. Before the research begins

Researchers should ensure that the work they wish to carry out is research; the following link will support that decision making process: http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/ If the work is not research, and can be defined as audit or service evaluation/development, this SOP does not apply. Research is designed and conducted to generate new knowledge. Under the Research Governance Framework all clinical research requires a sponsoring organisation and relevant permissions in place prior to the study commencing. Much of this research will also require ethical approval, and there may also be other authorisations required, depending on the type of research being conducted. There are national systems for gaining permissions/authorisations and websites describing those systems should be used as reference for those processes. For studies delivered at UH Bristol, the Research Management Office (RMO) will provide advice and guidance in navigating these, where required.

4.1.1 Funding

Any applications for funding associated with the research must be discussed with the R&I department to ensure costs are appropriately covered; please contact the Research Grants Manager. Please refer to the Developing and Designing your study SOP for further details. Please note funding must be in place before sponsorship is requested at UH Bristol.

4.1.2 Sponsorship

If you want UH Bristol to act as sponsor please refer to the UH Bristol Sponsorship SOP for the

application process. The regulations regarding clinical trials of investigational medicinal products (CTIMPs) differ slightly to other research, but the principles remain broadly similar. A sponsor is responsible for overseeing the conduct, management, monitoring and finances of research. For this reason it is essential that the sponsor agrees the final version of the protocol and associated documents before they are approved by the HRA, the MHRA, and any other bodies.

Researchers should usually approach their substantive employer to sponsor research. For student researchers, the university responsible for the academic course should be approached to sponsor the research in the first instance.

4.1.2.1. Amendments

Any changes to the protocol and associated documents after sponsorship must be agreed by the sponsor in advance of those changes being made. In conjunction with the study team, the sponsor will determine and document whether protocol amendments are substantial or not, prior to authorisations being sought. Further information on submitting amendments for UHBristol sponsored research can be found in the UH Bristol Sponsorship SOP and its appendices.

4.1.3 HRA approval

Health Research Authority website 2016:
'HRA Approval is the new process for the NHS in England that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK Health Departments' Research Ethics Service'

All proposed research within the NHS (e.g. using patients, staff or NHS facilities) must obtain HRA approval. More information on the submission process can be found on the HRA website:

http://www.hra.nhs.uk/research-community/applying-for-approvals/hra-approval/

4.1.4 NHS research ethics committee (REC) approval

Some research carried out in the context of the NHS is exempt from the requirement for NHS REC approval. See http://www.hra-decisiontools.org.uk/ethics/ to determine whether you need to apply for NHS REC approval. Different types of NHS RECs review different types of research proposals, and there are full details on the HRA website (given below).

Your research may require a different type of ethical review. These are provided by the Gene Therapy Advisory Committee, the Social Care Research Ethics Committee, the Ministry of Defence Research Ethics Committee and the Higher Education Institution (HEI) Research Ethics Committees.

For detailed information for researchers about REC approval and the types of NHS RECs, please see the HRA website, here: http://www.hra.nhs.uk/research-community/applying-for-approvals/research-ethics-committee

Please note only a single submission through IRAS is required for both HRA and REC review (if required). Further information can be found on the HRA website.

4.1.5 Capacity and Capability Confirmation at participating sites

For all participating sites in England an assessment of capacity and capability must be undertaken

by the local Research & Development office (at UH Bristol the R&I department) prior to the research commencing at the site. Further information on this process can be found on the HRA website: http://www.hra.nhs.uk/resources/hra-approval-nhs-organisation-guidance/#NHS

Please note sites outside England have different processes – please liaise with the local Research & Development department for further guidance on assessment requirements.

4.1.6 Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) For CTIMPs

CTIMPs require authorisation from the MHRA before they can proceed. Details about the procedure for application are available on the MHRA website (https://www.gov.uk/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk). For support and advice in preparing the application, which is done using IRAS, please liaise with the sponsor in the first instance.

4.1.6.1 Amendments to the protocol: If the protocol which has been approved by the MHRA is to be substantially amended, permission from the MHRA to do so must be sought, once the sponsor has agreed. This ensures that the clinical trial being conducted is the one which has been approved by the MHRA. Adequate notice must be given prior to submission of amendments in order for proper review to take place by the sponsor; this should be not less than one week. The MHRA also requests payments to review amendments therefore please consider this in your costings and whether an amendment is necessary.

4.1.7 Other authorisations

There may be other authorisations required prior to the start of the trial, depending on the type of research being carried out.

For research requiring CAG (confidentiality advisory group) approval see:
http://www.hra.nhs.uk/resources/confidentiality-advisory-group/

For research involving the administration of radiopharmaceuticals or sealed radioactive sources, the ARSAC notes for guidance should be used, found at:
https://www.gov.uk/government/publications/arsac-notes-for-guidance

For research involving a clinical investigation of a non CE marked medical device authorisation from MHRA devices is required. More information can be found:
https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

If it is unclear which other authorisations are required consult with the sponsor in the first instance, and the UHBristol Research Management Office for advice.

4.2. After Trial commencement

There are a number of other events which require notification/discussion with the MHRA (and REC) after trial commencement, listed below.

4.2.1. Suspending your research, then restarting it

If a CTIMP has to be suspended, the sponsor, MHRA and REC must be notified. The CI or delegated representative within the research team must contact the sponsor immediately to discuss this, and ensure the appropriate steps are taken to inform the REC/MHRA of the halt within the defined timeframes (at the latest within 15 days). Details of the process to

halt/suspend and restart a trial are found here: https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#suspend-or-terminate-a-trial. Documents found on the MHRA website should be used as a guide to inform the discussion between sponsor and research team about suspending the trial. All discussions must be documented, and this can be done using the form appended to this SOP, appendix 1.

For non CTIMP research, the REC must be notified. The CI or delegated representative within the research team must contact the sponsor immediately to discuss this, and ensure the appropriate steps are taken to inform the REC of the termination within the defined timeframes. For further details, http://www.hra.nhs.uk/resources/during-and-after-your-study/ All discussions must be documented, and this can be done using the form appended to this SOP, appendix 1.

4.2.2. Terminating your research.

If a CTIMP has to be terminated, the sponsor, MHRA and REC must be notified. The CI or delegated representative within the research team must contact the sponsor immediately to discuss this, and ensure the appropriate steps are taken to inform the REC/MHRA of the termination within the defined timeframes (at the latest within 15 days). For further details, see https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial. Documents found on the MHRA website should be used as a guide to inform the discussion between sponsor and research team about terminating the trial. All discussions must be documented, and this can be done using the form appended to this SOP, appendix 1.

For non CTIMP research, the REC must be notified. The CI or delegated representative within the research team must contact the sponsor immediately to discuss this, and ensure the appropriate steps are taken to inform the REC of the termination within the defined timeframes. For further details, http://www.hra.nhs.uk/resources/during-and-after-your-study/. All discussions must be documented, and this can be done using the form appended to this SOP, appendix 1.

4.2.3. Urgent Safety Measures for a CTIMP

If there are any safety issues which put a patient at risk during a CTIMP the MHRA must be notified immediately. Please refer to the Safety Reporting SOP for full details of how to process urgent safety measures. For further details, see https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#report-an-urgent-safety-issue .

4.2.4. Development Safety Update Reporting

Annual reports must be submitted to the MHRA in relation to the investigational medicinal product(s) in use. Please see UHBristol's Research Safety Reporting SOP for details of how this must be managed for our sponsored studies. Reports are usually due on the anniversaries of the date the MHRA authorisation was issued. Technical details for the submission can be found on the MHRA website: https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#submit-development-safety-update-reports-dsurs

4.2.5. Annual Safety and Progress reports

Annual safety and progress reports are required to be submitted to the ethics committee as a condition of the favourable opinion. Failure to do so can invalidate the favourable opinion. Both the progress and safety reports are due on the anniversaries of the date the REC favourable opinion was given. Further information on annual reporting requirements to RECs can be found: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

4.2.6. Serious Breaches

Serious Breaches must be notified to the MHRA, in accordance with their guidance, which can be found here: https://www.gov.uk/good-clinical-practice-for-clinical-trials Please refer to the managing breaches SOP for full details of how to process breaches.

4.2.7. End of trial

The MHRA (where applicable) and the REC must be notified that a trial has ended, within 90 days of the end of the trial, using a *Declaration of End of Trial Form*. Following that, an *end of trial study report* must be submitted to the MHRA (where applicable) and the REC within a year of the end of the study. See https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial and http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/notifying-the-end-of-study/ for details of both of these processes.

Where UHBristol is sponsor, each of these must be agreed by UHBristol R&I department prior to submission. A minimum of two weeks prior to the submission deadline, the report/form must be submitted to R&Dsponsorship@uhbristol.nhs.uk, so that the sponsor can agree and authorise submission.

4.2.8 Publishing results on the European Clinical trials Database (EudraCT)

For CTIMPs, in accordance with the commision's guidelines it is mandatory for the sponsor to post trial results in EudraCT http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

Where UH Bristol is sponsor, preparing these results will be delegated to applicable personnel within the research team.

5. Dissemination and training in the SOP

5.1. Dissemination of this SOP

5.1.1. New SOPs and new versions of existing SOPs: The Research Operations Manager will be responsible for ensuring authorised SOPs are uploaded to the DMS in line with Trust policy and on the R&I website as described in the SOP "Authorship, review, revision and approval of research procedural documents produced by research & innovation". Internal Trust Staff are expected to use the DMS to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given via the following routes:

- Inclusion in the R&I e-bulletin (monthly)
- Direct email to Research Leads, Research Unit Managers and Band 7 staff for onward cascade
- Direct email to Chief Investigators of CTIMPs sponsored by UHBristol
- Direct email to the Head of Research Governance at the University of Bristol (as relevant)

5.2. Training in this SOP

5.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5.2.2. The training log within the Site File/Trial Master File should be completed to document

that members of staff have read and understood the content of the SOP and its amendments.

6. **Appendices follow after the end of this document, and are listed below:**
    - **Appendix 1 - File note for discussions between sponsor and research staff**

IMPORTANT NOTE:
This procedure has been screened for equality impact; it was not assessed as having adverse effects on any section of the community.

RELATED DOCUMENTS	Research Safety Reporting SOP Developing and Designing Your Study SOP Research Training SOP Investigator Oversight SOP Authorship, Review, Revision and Approval of Research Procedural Documents Produced by Research & Innovation SOP Sponsorship SOP Monitoring and Oversight of Research SOP Capacity and Capability Review SOPManaging Breaches SOP
QUERIES	Research Operations Manager or Research Management Facilitators - Research & Innovation Department via 0117 342 0233

Appendix 1 File note for discussions between sponsor and research staff

Date of conversation:	UHBristol study number:
Study Title:	
Discussions between (names and roles:	
Subject of discussion:	Urgent safety measures (Serious) Breach Suspension of Trial Termination of Trial Other (delete as applicable)
Issues:	
Background:	
Proposed actions:	
Next steps:	

NB: If a paper copy is generated, it should be signed by the CI and the sponsor to indicate agreement with the contents. If the document is shared by secure email between the two parties, this is not required.