Standard Operating Procedure

S13 – HRA AND OTHER REGULATORY APPROVALS Version No 4	
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Controlled document

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DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

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Full History			
Version	Date	Author	Reason
1.0	28/03/2012	Assistant R&D Manager	New SOP
1.1	06/01/2014	Assistant R&D Manager	Minor typographical errors and updating website links. Updated format of SOP template.
2.0	August 2017	Senior Non-Network R&D Facilitator	Renamed. Moved into Trust format. Updated to incorporate the introduction of HRA approval and to also include other regulatory approvals.
3.0	September 2020	Senior Research Facilitator	Minor clarifications re name changes of documents.
4	September 2023	Senior Research Facilitator	Minor clarifications and update on National Regulations and approval processes.

Associated Trust Policies/ Procedural documents:	Research & Development Policy R&D/Protocol Amendments/S02 R&D/CTIMP Sponsorship/S09 R&D/Applying for Trust Approval/S21
Key Words:	HRA REC MHRA IRAS

In consultation with:

- Quality Assurance Group (July 2017)
- Senior Network R&D Facilitator (July 2017)
- Quality Assurance Group (September 2020)
- Quality Assurance Group (September 2023)

Contents

KEY POINTS OF THIS PROCEDURAL DOCUMENT:

- Health Research Authority (HRA) and Health and Care Research Wales (HCRW) applies to all project-based research taking place in the NHS in England and Wales. Studies led from England or Wales with sites in Northern Ireland or Scotland will be supported through existing UK-wide compatibility systems.

- Research Tissue Banks and Research Databases do not use HRA Approval and should continue to apply for ethical review using the appropriate forms in IRAS

- All applications for HRA review are prepared using the Integrated Research Application System (IRAS).

1 INTRODUCTION

Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval is the process for the NHS in England and Wales that brings together the assessment of governance and legal compliance. It replaces the need for local checks of legal compliance by each participating site in England and Wales. Participating organisations will focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.

The HRA assessment considers the following components:

- Compliance with legislation and HRA Assessment standards
- Contract assurance
- Study Delivery arrangements
- Clinical support technical assurances for pharmacy and radiation (to follow in 2016)
- The need for Principal Investigators, Local Collaborators or neither

Sponsors should check whether review by other bodies might be required for their study and to determine whether additional applications and approvals are therefore needed, for example, Research Ethics Committee (REC) approval. An independent REC opinion is included in the HRA Approval, where required.

2. PURPOSE

This Standard Operating Procedure (SOP) covers:-

- What research needs to be reviewed by the HRA
- Other regulatory approvals
- How to apply for HRA review

3. SCOPE

This SOP is applicable to Chief Investigators (CI) conducting research which involves humans, their tissue and/or their data.

It is applicable to R&D Facilitators setting up health-related research projects undertaken by the Trust which involve humans, their tissue and/or their data.

This SOP is also applicable to Trial Managers who have been delegated, by the CI, the responsibility for gaining regulatory approvals.

4. DEFINITIONS

ARSAC	Administration of Radioactive Substances Advisory Committee
CAG	Confidential Advisory Group
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
R&D GOG	Research & Development R&D Governance and Oversight Group
GTAC	Gene Therapy Advisory Committee
HEI	Higher Education Institution
HES	Hospital Episodes Statistics
HFEA	Human Fertilisation and Embryology Authority
HMPPS	HM Prison and Probation Service
HRCW	Health and Care Research Wales
HRA	Health Research Authority
HTA	Human Tissue Authority
IRAS	Integrated Research Application System
MARS	Medicines Administration of Radioactive Substances
MHRA	Medicines and Healthcare Products Regulatory Agency
MoDREC	Ministry of Defence Research Ethics Committee
MUGA	Multiple-Gated Acquisition scan
PET-CT	Positron Emission Tomography – Computed Tomography
PICs	Participant Identification Centres
REC	Research Ethics Committee
UKCEA	United Kingdom Ethics Committee Authority

5. DUTIES AND RESPONSIBILITIES OF STAFF

5.1 Sponsor

It is the Sponsor's responsibility to be satisfied that HRA Approval, and all other regulatory approvals, have been given, where required. The Sponsor takes primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.

5.2 Chief Investigator

It is the responsibility of the Chief Investigator to ensure that their health-related research project has been reviewed by the HRA. The CI may delegate the completion of the application/s to a member of the project team. If a project is to occur in the UK, the CI must be professionally based in the UK.

6. PROCEDURES

6.1 What Research needs to be reviewed by the HRA?

From April 2018, HRA became HRA and Health and Care Research Wales (HCRW) and now applies to all project-based research taking place in the NHS in England and Wales. Studies led from England or Wales with sites in Northern Ireland or Scotland will be supported through existing UK-wide compatibility systems, by which each country accepts the centralised assurances, as far as they apply, from the lead nation without unnecessary duplication. If the project is led from Scotland or Northern Ireland and involves NHS/HSC sites in England and/or Wales, you do not need to submit a separate application for HRA and HCRW approval. The project would need to go through the appropriate NHS/HSC permission process for that lead nation.

For guidance on which approvals are required please refer to What approvals and decisions do I need? - Health Research Authority (hra.nhs.uk)

Research Tissue Banks and Research Databases do not use HRA Approval and should continue to apply for ethical review using the appropriate forms in IRAS.

For educational studies which are taking place at a single NHS site in England, AND which do not require review by an NHS REC, it is usually the case that the NHS organisation and the University sponsoring the research will have an existing partnership and understanding about how these types of studies are handled. For these studies, there are two options depending on existing local arrangements:

- Where Universities and NHS organisations currently do not require an NHS R&D form to be submitted to the NHS R&D office but have alternative arrangements in place these may continue.

- Where Universities and NHS organisations currently do require an IRAS NHS R&D form to be submitted to the R&D office, then an application for HRA Approval should be made. A template Organisation Information Document and template Schedule of Events / Schedule of Events Costing Attribution Tool will not be needed as there is not likely to be the need to attribute funding. It is expected that the Sponsor will provide any advice and support to students using this process.

6.2 Other Regulatory Approvals

In addition to this SOP, please visit the website of each review body to check their requirements.

6.2.1 Research Ethics Committee

Research Ethics Committees review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical.
There are several different types of REC:

NHS Research Ethics Committees (NHS RECs):
NHS RECs safeguard the rights, safety, dignity and well-being of people participating in research in the NHS. They review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical.

Some of these RECs are also recognised for the purpose of reviewing clinical trials of investigational medicinal products (CTIMPs).

For studies being set up under HRA Approval, NHS REC review is undertaken as part of this process where it is required. A separate application for ethical review is not required. To help you decide whether your project needs NHS REC review, please refer to the HRA's decision tool.

Gene Therapy Advisory Committee (GTAC):
If your project is a gene therapy clinical trial you must apply to GTAC for ethical review.

For studies being set up under HRA Approval, GTAC review is undertaken as part of this process where it is required. A separate GTAC application is not required.

Social Care Research Ethics Committee:
The Social Care REC reviews social care research study proposals involving adults, intergenerational social care studies involving adults and children or families and some proposals for social science studies situated in the NHS. The Social Care REC does not consider any research involving clinical interventions. Such research should be reviewed by another appropriate REC within the UK Health Departments' Research Ethics Service. Social Care research involving only children is outside the remit of the Secretary of State for Health. Further guidance is provided on the National Social Care REC webpage.

Ministry of Defence Research Ethics Committee (MoDREC):
The ethical review of research funded by or sponsored by the MoD, including research involving the UK Armed Forces, is carried out by MoDREC. MoDREC is recognised by the United Kingdom Ethics Committee Authority (UKECA) to review clinical trials of investigational medicinal products involving subjects who are UK Armed Forces personnel recruited in a military setting, as well as Phase 1 trials in healthy volunteers conducted by the MoD or its agencies or contractors. It is also recognised as an Appropriate Body under the Mental Capacity Act 2005 for review of research involving UK Armed Forces personnel who are unable to consent for themselves.

Higher Education Institution (HEI) Research Ethics Committees:
Researchers in Higher Education Institutions (HEIs) are advised to check whether, under their institution's policy and internal arrangements, ethical review is required by their HEI research ethics committee.

6.2.2 Medicines and Healthcare products Regulatory Agency (MHRA)

The MHRA is responsible for the regulation of Clinical Trials of Investigational Medicinal Products (CTIMPs) and Medical Devices in research.

Clinical Trials of Investigational Medicinal Products (CTIMPs)

A Clinical Trials Authorisation (CTA) application must be made to the MHRA for all CTIMPs. Guidance on whether MHRA approval is required can be found on the following links:

- Algorithm_Clean__1_.pdf (publishing.service.gov.uk).
- Mock_examples_to_assist_with_determination_of_a_CTIMP.pdf (publishing.service.gov.uk)

Medical Devices

An application to MHRA Devices will be required where the study is a clinical investigation of a medical device undertaken by the manufacturer for CE marking purposes. This will be either an investigation of a non-CE marked product, or an investigation of a CE marked product that has been modified or is to be used outside its intended purpose.

MHRA approval is not always required in the case of:

- Medical devices manufactured "in-house" in a healthcare establishment;
- Clinician-led off-label use of a medical device.

In these cases, applicants are advised to contact MHRA Devices to discuss the purpose of the investigation and determine whether MHRA approval is required.

If you have a query which relates to a clinical investigation of a medical device you can contact info@mhra.gov.uk for support.

6.2.3 Confidentiality Advisory Group

The HRA's Confidentiality Advisory Group (CAG) provides independent expert advice to the HRA and the Secretary of State for Health on whether applications to access confidential patient information without consent should or should not be approved. You should apply to the CAG if you need to access: Identifiable patient information relating to people living in, or receiving healthcare in, England and Wales without explicit consent, prior to the disclosure of confidential information or Human Fertilisation and Embryology Authority (HFEA) Register Data.

You should contact the Confidentiality Advice Team if you are uncertain whether an application is needed by emailing cag@hra.nhs.uk.

Where applicants intend to link to national datasets, such as Hospital Episodes Statistics (HES) and cancer registry data, they will be expected to have contacted the data controllers for the dataset and discussed whether alternative methods which might limit the disclosure of confidential patient information without consent could be used. You will need to provide copies of this correspondence, and any other evidence to show that alternatives to access of confidential patient data without consent have been explored, as part of the supporting information for your application to CAG.

Please refer to the HRA website for guidance on applying for CAG approval. Confidentiality Advisory Group - Health Research Authority (hra.nhs.uk)

6.2.4 HM Prison and Probation Service (HMPPS)

If the project is with Prisons or Probation Trusts across England and Wales, an application to HMPPS will be required via the HMPSS National Research Committee (NRC). Please refer to the HMPSS website for more information. Please refer to the link for further information. Research at HMPPS - HM Prison and Probation Service - GOV.UK (www.gov.uk).

6.2.5 Administration of Radioactive Substances Advisory Committee (ARSAC)

Under the Medicines (Administration of Radioactive Substances) Regulations 1978 ('MARS'), administrations of radioactive medicinal products to humans must be conducted under certificates issued by the Health Ministers.

For research studies involving administration of radioactive materials which are additional to normal care, nuclear medicine professionals at each site require a research certificate from the Administration of Radioactive Substances Advisory Committee (ARSAC).

Procedures involving the administration of radioactive materials include:

- PET-CT
- Nuclear Medicine Bone Scans
- MUGA

Diagnostic X-rays, CT scans and DXA do not involve the administration of radioactive materials. For further guidance please refer to:

- Administration of Radioactive Substances guidance
- ARSAC website
- Guidance in IRAS including green “i” button question specific guidance

6.2.6 Human Fertilisation and Embryology Authority (HFEA)

Applications to the HFEA are required for:

Research involving human embryos and gametes
Under the Human Fertilisation and Embryology Act 1990, research involving human embryos or gametes requires a licence from the Human Fertilisation and Embryology Authority (HFEA) in addition to ethical review from a NHS REC. Licensing applications are reviewed by the HFEA Research Licence Committee.

Note: the application for this licence is not currently part of the Integrated Research Application System (IRAS). Please refer to the HFEA website for details of how to apply.

Disclosure of protected information from the HFEA Register
Under the Human Fertilisation and Embryology (Disclosure of Information for Research Purposes) Regulations 2010 (‘HFE Regulations’), certain protected information held on the register of the Human Fertilisation and Embryology Authority (HFEA) may be processed for research purposes subject to authorisation from the HFEA. For more information please refer to the HFEA website.

Note: The Human Fertilisation and Embryology Regulations apply to the whole of the UK.

6.2.7 Human Tissue Authority (HTA)

Under the Human Tissue Act 2004, storage of ‘relevant material’ (material from a human body consisting of or including cells) for scheduled purposes in England, Wales or Northern Ireland requires a licence from the Human Tissue Authority (HTA). The scheduled purposes include research in connection with disorders or the functioning of the human body.

The HTA does not approve individual projects or licence research activity itself but the organisations that store human tissue for research, including the following activities:

- Removal of relevant material from the deceased for the scheduled purpose of research.
- Storage of relevant material (from both the living and the deceased) for the scheduled purpose of research.

A licence is not required for storage in connection with a specific research project with approval from a REC. This exemption does not apply to tissue banks storing relevant material for use in future research. Where voluntary application is made to a REC for ethical review of a research tissue bank, a copy of the licence will be required by the REC as a condition of a favourable opinion.

6.3 How to apply for HRA Review

All applications for HRA review are prepared using the Integrated Research Application System (IRAS). Guidance on completing the form and supporting documentation is available within IRAS or from an R&D Facilitator. All applications must be accompanied by the research protocol and relevant documents, in accordance with the applicant's checklist (which must also be submitted). Application forms must be electronically authorised in IRAS.

All CTIMP and combined trials of an investigational medicinal product and an investigational medical device (IMP/Device trial) applications must now be made using the combined review service on IRAS. The researcher will make a single application using a new part of the IRAS which goes to both the MHRA and the REC at the same time. The application also goes for study wide review, such as HRA and HCRW approval, if the study is to take place in the NHS or Northern Ireland HSC. Please refer to Combined review - Health Research Authority (hra.nhs.uk) for guidance.
For medical device only studies, a submission is made to MHRA devices via IRAS. For any queries please contact info@mhra.gov.uk.

Studies may be eligible for HRA approval only and/or proportionate review by the HRA rather than a full REC review, if there are no matters of ethical concern. The Health Research Authority (HRA) provides two linked, online decision tools to assist you in determining whether your project is classified as research and whether it requires ethical review by a NHS Research Ethics Committee (REC). These tools are available at: • Is my study research? (hra-decisiontools.org.uk)• Do I need NHS Ethics approval? (hra-decisiontools.org.uk)

The Proportionate Review Service provides an accelerated review via email correspondence, teleconference or face to face meeting by a sub-committee rather than at a full meeting of a REC. Please refer to the following link for guidance on whether your study qualifies for Proportionate Review: Proportionate_Review_Toolkit.

The following steps should be followed for HRA/REC approval when preparing an application to IRAS:

1. Sponsorship is confirmed by R&D – see S09
2. R&D Facilitator advises Researcher on IRAS, HRA process and other approvals needed,
3. Researcher completes application via IRAS and finalises study documents
4. R&D reviews application and study documents
5. CI and Sponsor Representative e-sign the application
6. If study reviewed by a full REC, researcher books the REC via an online booking service. Researcher receives email confirming booking and REC reference number and adds to IRAS form along with REC name and submission date. Researcher then electronically submits the IRAS form.

This must be done on the same day as making the booking.

7. If study submitted for Proportionate Review, a member of HRA staff undertakes a thorough pre-screen to check that the application is eligible. If it's decided that the application needs full REC review, the researcher will be contacted within two working days and arrangements made for the application to be transferred.
8. Researcher receives correspondence from the HRA and REC (if applicable) regarding whether the application is valid.
9. HRA review the application internally. Researcher attends REC meeting (if applicable). If proportionate ethics review, the application is reviewed internally by members of a sub-committee. HRA and REC review are completed in parallel.
10. Researcher receives correspondence regarding HRA and Ethics approval (if applicable).
11. R&D confirms the Royal Devon University Healthcare NHS Foundation Trust and all its designated delivery sites capacity and capability to participate in the study. Where the study is multi-centered or if Participant Identification Centres (PICs) have been set up, the researcher must seek approval from the R&D from every research site before they can be given the 'green light' on behalf of the Sponsor to start the study. Please refer to SOP S21.

6.4 Amendments to HRA Approval

Refer to SOP SO2 on Submitting Protocol Amendments

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the Royal Devon website shortly after having been released.

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

7.3 *If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.*

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Has the SOP been followed by the CI or their delegate in applying for the relevant regulatory approvals?	R&D signature on IRAS form confirms that this has been checked.
2.	Were the regulatory approvals which were applied for correct?	Compare the approvals which were originally requested on the IRAS form to the approvals received.
3.	Received all regulatory approvals before CC&C.	Check approval letters in R&D file to ensure CC&C was issued after regulatory approvals.

8.2 Outcomes from audit will be presented to the Governance and Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the Royal Devon website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

10.1 **Related SOPs**:

R&D/Protocol Amendments/S02

R&D/CTIMP Sponsorship/S09

R&D/Applying for Trust Approval/S21

R&D/Reporting required for CTIMP Studies/S31

10.2 **Related Websites:**

1. Health Research Authority http://www.hra.nhs.uk/
2. Medicines for Human Use (Clinical Trials) Regulations 2004, Schedule 1, Part 2/3 The Medicines for Human Use (Clinical Trials) Regulations 2004 (legislation.gov.uk)Research Governance Framework for Health and Social Care UK Policy Framework for Health and Social Care Research - Health Research Authority (hra.nhs.uk)
3. IRAS - https://www.myresearchproject.org.uk/
4. GTAC http://www.hra.nhs.uk/resources/applying-to-recs/gene-therapy-advisory-committee-gtac/