STANDARD OPERATING PROCEDURE 5 part 1
Gaining Initial Ethical Approval for Research Studies

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Revision Chronology:	Effective date:	Reason for change:
Version 5.0	16 February 2023	Biennial review: Updates to application process. Addition of section on international sites.
Version 4.0	3 December 2020	Title, scope and format change to detail how to obtain initial ethical approvals only. Amendments and ongoing communications with authorities are now covered in SOP 5 part 3 'Communication with Approval Bodies' and SOP 6 'Amendments'
Version 3.1	24 February 2020	Biennial review: Updates to required documentation for approvals, updated application process flowchart QA requirement to review all amendments to WCTU studies. Change to new format
Version 3.0	1 December 2017	Updated to include new HRA approvals procedures including NHS Trust permissions.
Version 2.3	1 February 2016	Biennial review: Web links updated (HRA). Changes to REC booking procedure. Addition of requirements for trial registration, electronic authorisations and amendment notifications for NIHR funded projects.
Version 2.2	15 August 2013	Biennial review: Process flowcharts and web links updated. Minor text changes.
Version 2.1	21 March 2011	New guidance on notifying protocol amendments (section 3.3.2). Addition of Appendix 1.
Version 2.0	21 May 2010	Update of SOP to reflect new application system (IRAS). Remove information on R&D approval process to create new SOP.
Version 1.1	31 January 2008	Change references from COREC to NRES. Changes to application processes, to include process for amendments detailed.
Version 1.0	March 2006	

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1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to describe the processes required to obtain all relevant approvals from a Research Ethics Committee (REC) and/or the Health Research Authority (HRA) for commencing a research study and is applicable to all University of Warwick staff.

This SOP does not cover the details for gaining University Ethics approvals from the Biomedical and Scientific Research Ethics Committee (BSREC) or Humanities and Social Sciences Research Ethics Committee (HSSREC). For further information regarding University RECs, please refer to the Research & Impact Services webpages.

2. Definitions

Research	The attempt to derive generalisable or transferable new knowledge to answer or refine relevant questions with scientifically sound methods. A key feature of research is that it is intentionally planned and designed using documented methodology to answer a specific question which will allow results to be extrapolated or applied from the study sample to a larger population. Research has clearly defined aims and objectives.
Approval (in relation to Research Ethics Committees (RECs))	The affirmative decision of the REC that the study has been reviewed and may be conducted at the institution site(s) within the constraints set forth by the REC, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Research Ethics Committee (REC)	An independent body constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a study and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the study protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the study participants.
Integrated Research Application System (IRAS)	System for applying for the permissions and approvals for health, social and community care research in the UK.
Health Research Authority (HRA)	An extension of the Department of Health and Social Care in the UK set up to streamline and regulate different aspects of health and social care research. The HRA manage the UK NHS Research Ethics Committees.

3. Background

Ethical approval of research studies is a central theme of the Declaration of Helsinki, the UK Policy Framework for Health and Social Care 2017 and Good Clinical Practice guidelines.

To understand whether ethical approvals are required, researchers must determine whether a study/project is classed as research, and therefore whether it should be managed as such. The responsibility for determining whether a project is classed as research lies with the managing organisation. To assist in determining whether a project is research, the HRA has developed a decision tool.

For WCTU managed studies, the QA team can provide advice to research teams. For other Warwick studies, contact the Research Governance Team in R&IS for advice.

Where a project in the NHS will not be managed as research there is no need to apply for HRA Approval or to an NHS REC. However, you should contact the clinical governance or research and development (R&D) office of the organisation where the project will be conducted to discuss what other local review arrangements or sources of advice may apply. Studies not requiring NHS REC approval but involving human participants, their tissue or data may require ethical approval from a University of Warwick REC such as the Biomedical & Scientific Research Ethics Committee (BSREC) or the Humanities & Social Sciences Research Ethics Committee (HSSREC). For further information please see the 'Applying for Ethics' pages on the R&IS webpages.

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, undertaken by dedicated HRA and HCRW staff, with the independent REC opinion provided through the UK Research Ethics Service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England and Wales.

If your project is led from Northern Ireland or Scotland and involves NHS/HSC sites, then you will not apply to the HRA. You should apply through the appropriate NHS/HSC permission process for that lead nation. For any new studies that are led from Scotland or Northern Ireland, but have English and/or Welsh NHS sites, the national R&D coordinating function of the lead nation will share information with the HRA and HCRW Approval teams, who can issue HRA and HCRW Approval for English and Welsh sites and thereby retain existing compatibility arrangements.

HRA and HCRW Approval applies only to 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. Full guidance is available on IRAS.

The table below summarises scenarios when HRA approval, NHS or other REC approval may be required:

	HRA and HCRW Approval required?	NHS REC Approval required?	University BSREC/HSSREC Approval required?
Research- involving NHS patients, their identifiable data or tissue	Yes	Yes	No
Research involving NHS/Social care staff only	Yes	No	Yes
Research involving NHS patients and staff	Yes	Yes	No
Research in the community (e.g., schools)	No	No	Yes
Research limited to use of previously collected non-identifiable patient data	Yes (HRA only)	No	Yes
Research limited to use of previously collected non-identifiable human tissue collected <u>with</u> consent for use in research	Yes – if obtaining directly from NHS dept. e.g., pathology No- if from established NHS tissue bank or source outside NHS	No	Yes (unless supplied by established tissue bank which issues own ethics approval)
Research limited to use of previously collected non-identifiable human tissue collected <u>without</u> consent for use in research	Yes	Yes	No
Research limited to use of acellular material (e.g., plasma, serum, DNA,) extracted from tissue previously collected in the course of normal care, provided that the patients or service users are not identifiable	Yes	No	Yes
Research involving the premises or facilities of care organisations only	Yes	No	Yes

Clinical Audit or Service Evaluation	No	No	Yes

For further information about HRA and REC approvals or any additional approvals that might be required see the 'What approvals do I need?' page of the HRA website. If uncertainties remain as to which approvals and decisions are required from the HRA, email the HRA queries line

Researchers are also advised to refer to the University of Warwick Ethics and Research Governance Code of Practice

4. Procedure

4.1 Responsibilities

Chief Investigator (CI)	• Making the application for ethical review of the research protocol (Applications may not be submitted by the sponsor(s) on behalf of the CI) • May designate a member of staff to prepare the submission but retains responsibility for any application and is required to sign the completed application form • It is recommended that the CI and an appropriate member of the study team attend the REC meeting to clarify any queries that may arise
Sponsor	• Review and approval of the proposed study • Sign-off of the completed application • Oversight of the project

4.2 When?

It is a requirement that written approval must be obtained from the HRA (to include relevant REC approval) before the first participant is approached about the study and before the start of any screening procedures.

Multi-site studies within the NHS require approval from a REC and subsequent management assessment by the local NHS Research & Development (R&D) office at each site to confirm their capacity and capability to undertake the study.

4.3 How?

Applications for ethical review are made using the Integrated Research Application System (IRAS) and comprehensive guidance on preparing and submitting applications is available.

Any subsequent substantial amendment to the study protocol will also require approval. For full details see SOP 6 'Amendments to Approved Study Documents'.

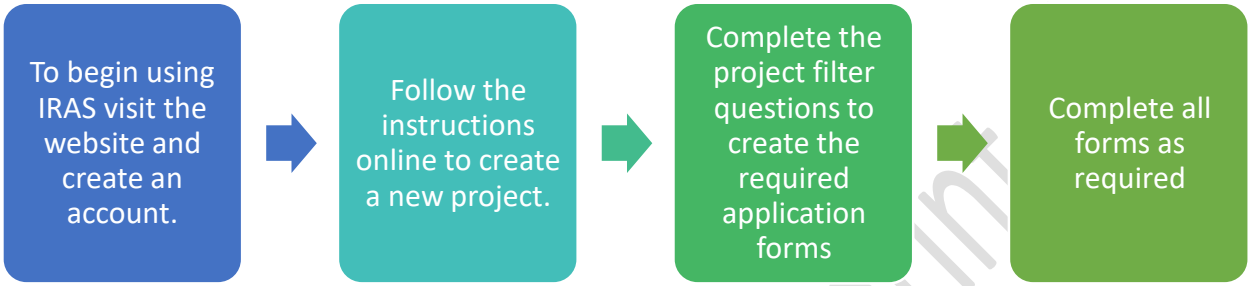
4.3.1 Initial Approval

IRAS captures the information needed to obtain the relevant approvals from the following **review bodies** and prevents having to enter the same information into each form:

- Administration of radioactive Substances Advisory Committee (ARSAC)
- Gene Therapy Advisory Committee (GTAC)
- Medicines and Healthcare products Regulatory Agency (MHRA)

- Health Research Authority (HRA) and Health and Care Research Wales (HCRW) for projects seeking HRA Approval NHS / HSC R&D offices
- NHS / HSC Research Ethics Committees
- NHS / HSC R&D offices
- Confidentiality Advisory Group (CAG)
- His Majesty's Prison and Probation Service (HMPPS)
- Social Care Research Ethics Committee

An e-learning module is available on the IRAS site to guide researchers through the processes required.



The study CI is responsible for ensuring the application forms are correctly completed.

During the completion process, access to the forms may be transferred to an appropriate designee for review and specialist input into the text.

Clinical Trials of Investigational Medicinal Products (CTIMPs) also require approval from the MHRA. For full details of the MHRA application process refer to Warwick SOP 5 part 2 'Gaining Initial Regulatory Approvals'.

To apply for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR CRN Portfolio, study teams should select yes to question 5b of the IRAS project filter. The full IRAS submission should then be submitted for HRA Approval, as usual. When the submission is deemed valid by HRA, information from the IRAS submission will then automatically be shared with the NIHR CRN and used to determine whether the study is eligible for NIHR CRN support and inclusion on the NIHR CRN Portfolio. The NIHR CRN will notify you of their decision by email.

The CRN have an Early Contact and Engagement Team, available for portfolio adopted studies (and studies fulfilling the criteria for adoption, but have not yet been formally accepted), who can provide support in the development, set-up and delivery of research studies. To access this support, contact the team as early in the development process as possible via: supportmystudy@nihr.ac.uk

Further information on the NIHR CRN Portfolio can be found at: CRN Portfolio | NIHR

The HRA website provides comprehensive guidance on preparation of study documentation: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/prepare-study-documentation/.

For non-commercial studies researchers are now required to complete and include in any application to the HRA the Organisation Information Document (OID) for each type of research site in the study. A copy of the model Non-Commercial Agreement (mNCA) document is also required for studies where the OID does not form the basis of the agreement with study sites. Further guidance on completing these documents is available and advice can be sought from the Grants and Contracts Team in R&IS via rssgrantscontracts@warwick.ac.uk or wmsgrantssupport@warwick.ac.uk for Warwick Medical School and WCTU lead studies.

All of the required supporting documentation must be attached to the application. Ensure they are all dated and version controlled. Lack of date and version number is one of the main reasons that applications cannot be validated.

4.3.1.1 Proportionate Review

If the study is considered to present no material ethical issues (presenting minimal risk or burden for participants e.g., research using data or tissues that are anonymous to the researcher, research involving questionnaires only which do not include highly sensitive areas), then the study may be eligible for review under the Proportionate Review Service.

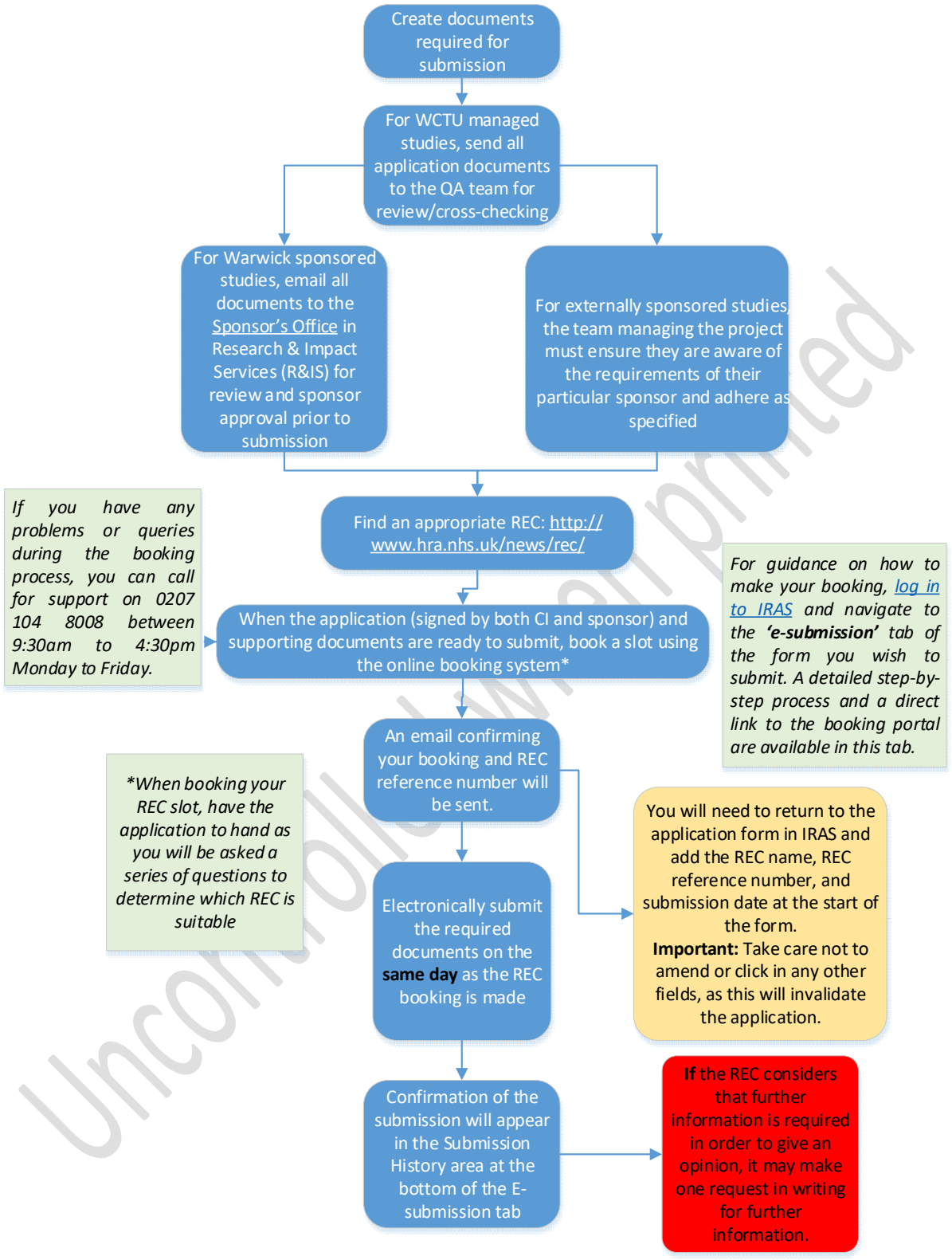
The Proportionate Review Service (PRS) provides an accelerated, proportionate review of research studies via email correspondence, teleconference or at a face-to-face meeting by a sub-committee (comprised of experienced expert and lay members) rather than at a full meeting of a REC.

For an application to be potentially suitable for proportionate review, it should fit one of the categories listed in the 'No Material Ethical Issues Tool' which can be found on the HRA website. Such studies are reviewed within 14 days of receipt of a valid application. Further information and guidance are available on the HRA website.

4.3.1.2 Submission of initial application

Pre-submission advice can be sought from local HRA Offices: http://www.hra.nhs.uk/contact-us/.
To ensure applications are 'valid first time' the HRA has developed guidance which is available on the research planning section on their website

The submission process is detailed in the flow chart:



N.B. The majority of supporting documents (which must be appropriately named to include version number and date in the document file name and within the document itself (generally in the footer)) that accompany an application are specified in the applicant's checklist in the IRAS system which is automatically generated but may require amending to include all relevant documents. A full list

(including templates) of the supporting documents that need to be submitted to the HRA for approval (including additional documents not listed on the IRAS checklist) are available.

Required documentation includes the Organisation Information Document (OID) which must be reviewed by the study sponsor prior to submission (this replaces the Statement of Activities previously used in England and Wales and the Site-Specific Information (SSI) Forms previously used in Scotland and Northern Ireland) and Schedule of Events/Schedule of Events Cost Attribution template (SoECAT) documents which are also required as supporting documents for the HRA approval process. The SoECAT submitted to REC must be validated by the local CRN prior to submission. IRAS provides additional guidance and template documents.

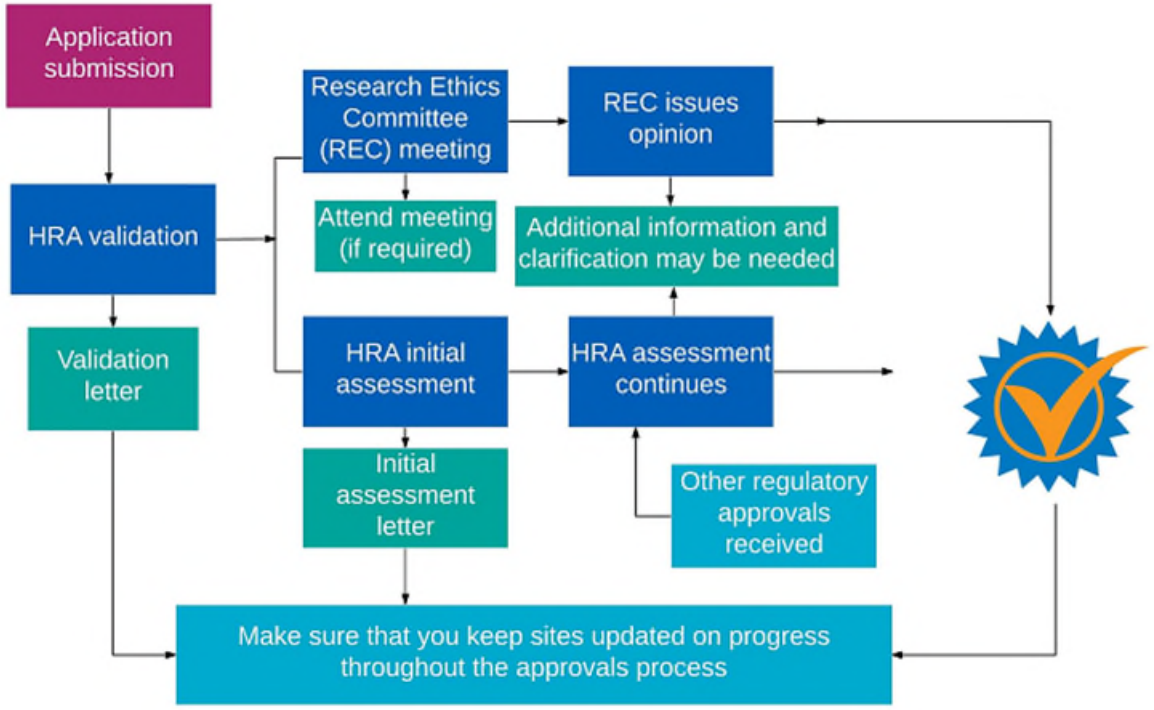
N.B. Ensure all supporting documents (e.g., protocol, PIL etc.) have obtained the relevant internal approvals. For studies managed by WCTU, all key documents must be approved via the Q-Pulse system or via a professional email account prior to submission. For further details, see SOP 45 'Document Management'.

4.3.1.3 REC and HRA Review Process

Following the submission of a valid application, the REC is required to give an ethical opinion within 60 calendar days. If you chose not to attend the first meeting available, the 60 calendar days will start from the cut-off date for the meeting (which is 14 calendar days before the meeting date).

Where the REC considers that further information is required in order to give an opinion, it may make one request in writing for further information. The period of 60 days will be suspended pending receipt of this information.

The flowchart below details the main steps in gaining REC and HRA approval:



NOTE: Where a study is using primary care services either to identify potential participants (using Patient Identification Centres (PICs)), or act as research site, the local Primary Care Clinical Research

Network (CRN) should be contacted as soon as possible to allocate a facilitator and assist in the process of gaining approvals. The CRN will contact Clinical Commissioning Groups (CCG) in their region and identify GP practices to approach to take part in the study. The CCGs approached should be named in the IRAS form, (you will need to answer YES to question A73 to reveal the secondary PIC questions and include the contact details and activities of PICs associated with research sites (except where the activity is limited to displaying leaflets or posters only)). A process called 'Assess, Arrange, Confirm' (AAC) is commenced by the CRN to green light activities within the CCG area. The CRN will confirm via email when this process is complete, then individual GP practices can be approached, and a confirmation form or contract will be signed by the lead GP in each practice to confirm they are willing to take part in the study.

The HRA provide information about what to expect when attending a REC meeting on their website.

The NHS REC will examine and consider the following points:

- The suitability of the Investigator for the proposed trial, including their qualifications, experience, support staff, and available facilities.
- The data available on the drug, procedure or device under study.
- The suitability of the protocol, including the objectives of the trial, the potential for reaching sound conclusions with the smallest possible exposure of participants, and a weighing up of the possible risks and inconveniences with possible benefits to the patient and others.
- The suitability of the patient information, consent forms and procedures. They should also review publicly accessible study websites if applicable.
- Recruitment arrangements and access to health information, and fair participant selection.
- The provision for compensation and/or treatment in the case of injury or death of a participant if attributable to a clinical trial, any insurance or indemnity to cover the liability of the Chief Investigator (CI) and sponsor.
- The extent to which Investigators and participants may be rewarded and/or compensated for participation.

Following the REC meeting, the committee will provide one of the following outcomes:

- favourable opinion with standard conditions
- favourable opinion with additional conditions
- provisional opinion with request for further information
- provisional opinion pending consultation with referee
- unfavourable opinion

Detailed information on what these decisions mean can be found in the REC Standard Operating Procedures.

Only applications which receive a **favourable opinion** may commence trial activities, upon the assumption that any conditions stipulated in the opinion letter are met. Guidance on standard conditions to be met by CTIMPs and non-CTIMPs is available on the HRA webpages

HRA approval will be issued once all required approvals are in place. Note, that if your project is led from Northern Ireland or Scotland then you must ensure you have followed the NHS/HSC permission process for that lead nation, to ensure the necessary approvals are issued following REC favourable opinion.

4.3.1.4 Appeals against unfavourable opinion

If the application receives an unfavourable opinion and you do not feel it is possible to make all the changes required by the reviewing REC, you can appeal. If you have any queries or wish to discuss the content of the opinion letter, you should contact the REC manager or the named person in your decision letter. If your appeal goes ahead, arrangements will be made for the original application to be reviewed by a different REC. Further details are available.

4.3.1.5 Technical Assurances

a) Radiation Assurance

If additional radiation exposure is included in a study protocol, or if your protocol specifies the frequency, activity or processing for an administration that would otherwise be considered standard care, Radiation Assurance is a UK-wide process fully managed by the HRA to clarify the information regarding radiation exposures in study documentation prior to seeking ARSAC approval. Full details are available here.

b) Pharmacy Assurance

The Pharmacy Assurance process coordinates a single technical pharmacy review for eligible studies. The completed review can be used by all participating NHS/HSC sites across the UK to assess local capacity and capability in their pharmacy departments. Pharmacy assurance has been designed to streamline the local pharmacy review process, allowing sites to assess capacity and capability and open to recruitment sooner.

Note: Fees may be applicable for both radiation and pharmacy assurance services.

4.3.1.6 Site level process (NHS Management Permission Review)

Under the HRA Approval system, sponsors and NHS organisations are expected to work collaboratively so that the participating NHS organisations can confirm:

- that they have the capacity and capability to deliver the study
- that arrangements are in place to do so,
- that they are ready to start the study.

Before applying for HRA Approval the sponsor is expected to have identified potential participating sites and, in most cases, have discussed the project with local researchers and the research management staff supporting them. For University of Warwick sponsored studies this activity would normally be carried out by the CI and/or study team. Contact details for R&D staff at NHS organisations can be found on the NHS R&D Forum.

The process for setting up NHS sites will differ slightly depending on the lead nation for the study. For information relating to site setup and local processes, where the lead R&D office is located within one of the devolved nations, please refer to the relevant sections of the IRAS and HRA websites.

The documents required for study set-up, including REC and HRA approval, are shared with participating sites via the UK Local Information Pack (LIP). The LIP provides a consistent package to support study set-up and delivery across the UK and should be used for all studies with participating NHS/HSC organisations.

Following submission of your application, the HRA will issue an initial assessment letter which will state whether the LIP can be sent to sites.

N.B. The LIP should not be sent to sites until the HRA initial assessment letter has been issued. Details of the required contents of the LIP are available on the IRAS help pages.

In England and Wales, the HRA/HRCW does not provide documents to individual sites. The CI/sponsor is responsible for providing the LIP to local research teams, as well as to the relevant R&D Office and Local Clinical Research Network (CRN). For University of Warwick sponsored studies this activity will be carried out by the CI/study team. Guidance on sharing the LIP with participating sites in Scotland and Northern Ireland can be found on the IRAS website.

4.3.2 International sites

Where international sites are involved in a research study, ethical approval must be gained along with all necessary regulatory approvals and permissions as appropriate in accordance with local requirements. Evidence of local ethical approval is required by the coordination centre prior to any study related activities commencing in that country.

Procedures to open international sites should follow SOP 26 'Clinical Research Study Activation, Site Selection and Initiation'. Sponsorship, insurance, agreements/contracts and oversight arrangements (including monitoring) must be in place before any site is activated.

List of abbreviations

ARSAC	Administration of Radioactive Substances Advisory Committee
BSREC	Biomedical and Scientific Research Ethics Committee
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRN	Clinical Research Network
CTIMP	Clinical Trial of Investigational Medicinal Product
GTAC	Gene Therapy Advisory Committee
HMPPS	His Majesty's Prison and Probation Service
HRA	Health Research Authority
HCRW	Health and Care Research Wales
HSC	Health & Social Care
HSSREC	Humanities and Social Sciences Research Ethics Committee
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
LIP	UK Local Information Pack
MHRA	Medicines and Healthcare Products Regulatory Agency
mNCA	model Non-Commercial Agreement
NIHR	National Institute for Health and Care Research
OID	Organisation Information Document
PAF	Portfolio Adoption Form
PIC	Patient Identification Centre
PRS	Proportionate Review Service
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
WCTU	Warwick Clinical Trials Unit