STANDARD OPERATING PROCEDURE FOR NHS ETHICAL AND RESEARCH & DEVELOPMENT APPROVAL
(NWORTH 4.01)

Approvals

Principal Author
Name: D. Skelhorn  Signature: D. Skelhorn  Date: 10/09/2014

Quality Assurance Officer

NWORTH Director

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Telephone: 01248 388095  Email nworth@bangor.ac.uk  http://www.bangor.ac.uk/imscar/nworth
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2. Purpose

The purpose of this SOP is to document how to apply for NHS Research Ethics Committee (REC) and Research and Development approval for health-related research projects undertaken within the UK. It provides general information on the NHS REC system and outlines the steps that should be completed in the application process. It should be noted that the information within this SOP is only a summary. For detailed current guidance refer to: https://www.myresearchproject.org.uk/, http://www.hra.nhs.uk/about-the-hra/our-committees/nres/

3. Scope

This procedure applies to trials where NWORTH has undertaken the responsibility for ethics and R&D submissions; and applies to the process of obtaining approval for both CTIMPs and non CTIMPs. Where REC approval is sought for IMP research, compliance with NWORTH SOP 4.02 MHRA approval is also required.

4. Responsibilities

**Sponsor** is responsible for:

- ensuring all regulatory approvals are in place before a study begins at any site. This may be delegated to the CI or Director of NWORTH. The Director in turn may delegate to a suitably qualified person such as the Trial Manager (TM), Principal Investigator (PI) or a member of the NWORTH team depending on the nature of the study.

**Chief investigator** has overall responsibility for:

- the research,
- in a multi-site study, co-ordinating responsibility for research at all sites,
- all applications for ethical review should be signed and submitted by the CI, the CI is required to sign the final application.

**Trial Manager** is responsible for:

- supporting the CI and Trial Management Group (TMG) in the application. If a TM is not in post, this may be delegated to the NWORTH Trials Unit Manager,
- ensuring that sites taking part in the research complete the SSI form and obtain NHS R&D approval before site initiation and set up takes place in accordance with NWORTH site setup SOP 3.03,
- ensuring copies of all ethical and R&D approvals are within the Trial Master File (TMF) and relevant Investigator Site File (ISF) in accordance with NWORTH trial master file SOP 3.04.

**The PI** is responsible for:

- signing off the SSI form,
- ensuring both SSA and NHS R&D approval is obtained prior to starting the research at their site. In the case of a single-site study, the CI and PI will usually be the same person.
5. Procedure

5.1 Procedure Flow Chart

Determine the nature of the study and ensure all supporting documentation is prepared and available for submission (Ref. 3.02 Protocol development).

- Populate the IRAS form

Contact REC (See HRA website).

Electronically submit to REC with supporting documents and retain a copy for TMF.

Complete NHS R&D SSI Form on IRAS for each site.

Submit to R&D via NISCHR PCU with supporting documents (retain a copy for TMF).

All applications approved, study can commence.

Is there a change to the study?

- No: No action required
- Yes: Determine if the change is substantial (see NRES and MHRA websites for guidance and SOP 3.02 protocol development).

Substantial amendment?

- No: Update trial documentation where required and notify relevant parties of the change.
- Yes: Submit notice of substantial amendment to relevant bodies (see HRA & MHRA website for guidance).

Only introduce change when all relevant bodies (REC, R&D and MHRA if required) have approved change.
5.2 Background

Ethical review is one of a series of safeguards intended to protect individuals as described in the Research Governance Framework for Health and Social Care on the Department of Health's website.

The primary function of a Research Ethics Committee (REC) when considering a proposed study is to protect the rights, safety, dignity and well-being of all actual or potential participants. The remit of RECs is described in the Department of Health's guidance, Governance Arrangements for Research Ethics Committees (GAfREC) which is located on their website http://www.hra.nhs.uk/resources/research-legislation-and-governance/governance-arrangements-for-research-ethics-committees/.

In addition to ethical review, the scientific value of all proposed research must be considered by NHS R&D departments at all relevant research sites. NHS R&D departments have the responsibility for assessing the safety, suitability and capacity for conducting the research within their own organisation, and for carrying out a Site Specific Assessment (SSA). Ethical approval and approval from relevant NHS R&D departments must be obtained before any study can start at any site.

Ethical approval from the appropriate NHS REC is required for any research involving staff, patients and users of the NHS. This includes all potential research participants recruited by virtue of the patient or user's past or present treatment by, or use of the NHS. It includes NHS patients treated under contracts with private sector institutions; individuals identified as potential research participants because of their status as relatives or carers of patients and users of the NHS, as defined above; access to data, organs or other bodily material of past and present NHS patients; fetal material and IVF involving NHS patients; the recently dead in NHS premises; the use of or potential access to NHS premises or facilities. Selection of participants by virtue of the fact that they are employed by or work within an NHS organization also requires ethical approval.

5.3 Research involving two or more Centres

For research involving two or more centers, approval must be sought from an appropriate Research Ethics Committee (REC). REC approval applies to all NHS organisations involved in the research. Once a valid application is received by the appropriate REC, applications for SSAs for each site should be submitted to each NHS R&D department.

5.4 National Research Ethics Service (NRES)

All research taking place within a healthcare setting must be reviewed independently to ensure that it meets ethical standards to protect participants and the organizations where the study will be conducted. NRES is a core function and directorate of the Health Research Authority.

The NRES works to maintain a UK-wide system of ethical review that protects the safety, dignity and well being of research participants, whilst facilitating and promoting ethical research within the NHS. Detailed information on the types of study that require ethical approval are available on the HRA web site http://www.hra.nhs.uk/about-the-hra/our-committees/nres/
All applications for ethical approval must be made using the on-line Integrated Research Application System (IRAS).

5.5 Applying for REC approval

Guidance notes on submitting an application are available on the NRES website. To make an application go to https://www.myresearchproject.org.uk/Signin.aspx

If you are a first time user, you will need to register for an account online, which is activated immediately.

It is important to follow the question-specific guidance.

All forms created in IRAS for submission to NHS RECs (except notices of substantial amendment, which should be submitted by email) should be submitted electronically from IRAS.

http://www.hra.nhs.uk/research-community/booking-submission-changes-spring-2014/

The NHS REC form (including GTAC, Social Care REC, Research Tissue Bank and Research Database variants) and non-NHS Site Specific Information (SSI) forms and their associated supporting documentation must be electronically submitted by the applicant from IRAS to the REC system.

Electronic submission must be completed on the same day as the booking is made. So applicants must ensure that their application is ready to submit (i.e. form checked, supporting documents attached and e-authorisations in place) before calling to book their application. Any pre-submission advice should continue to be sought from local HRA Offices.

Note that Notice of Substantial Amendment forms submitted to REC must be electronically authorised in IRAS; this will be checked at validation - See more at: http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/#sthash.AsD8OlJY.dpuf

The ethical review process has been summarised on the HRA website (Application Process Flowchart). The flowchart provides a clear map of the tasks involved, with links to other on-line resources relevant to each stage.

http://www.hra.nhs.uk/resources/applying-to-recs/nhs-rec-application-process-flowchart/

In summary:

- Once you have completed the application and have supporting documents, phone the Central Booking Service (CBS) to book in the application.
- Submit the application form and supporting documents electronically. This must be done on the same day as making your booking for ethical review.
- REC Coordinator validates application (5 working days).
- Valid Application – CI invited to REC meeting, or to be available by phone. Invalid application returned, booking process starts again.
• Application reviewed by the REC.
• Favourable Opinion (within 60 days).
• Provisional opinion (60 days clock stops).
• Modify application (60 day clock restarts).
• Modifications reviewed by Chair or Sub-committee.
• Favourable or Unfavourable Opinion (within 60 days).

Note: the 60 day clock is the clock that starts when the application is received by the REC office.

If it is a study involving an IMP or medical device, you must apply for clinical trial authorization (CTA) from the MHRA either at the same time as you make your REC application or in sequence (see NWORTH MHRA approval SOP 4.02 and MHRA website).

The REC application form for CTIMP has a space to enter the EudraCT number, which allows the REC to link your application for ethics approval to you application to the MHRA for a CTA. The EudraCT number is the mandatory reference number allocated by the European Medicines Agency (EMEA) for CTIMPs. Further details can be found on the MHRA web site.

If the research involves the use of patient identifiable information without consent, you will need to apply to the Patient Information Advisory Group (PIAG) after you have received a favorable REC opinion.

It is recommended that funding is secured and NHS R&D support in principle is obtained before making REC applications.

There are different types of NHS RECs across the UK that review different kinds of studies. To determine the appropriate REC for your study see information on the NRES website.

The application form can be saved and reloaded for further editing. A filter is used to specify which sections of the form you need to complete, i.e. multi centred, single centre etc.

Once an application is complete and ready to send, phone to book in the application to the Central Booking Service. Once the application has been booked you will receive an email confirming your booking and REC reference number; you must electronically submit your application, this must be done on the same day as making your booking for ethical review. Ensure that all supporting documents (see IRAS submission application check list) are prepared before booking. It is important to lock the form before submitting it to the REC. Once the form is locked, further changes to the application cannot be made.

There is no application fee for ethical review by an NHS REC. The application must be submitted by the deadline given by the REC to ensure it is reviewed at the designated REC meeting. Failure to submit by the deadline will result in your application being delayed and processed at a subsequent meeting.
A standard letter confirming validation or not, will be sent within 5 working days. For multi-centre studies, once the CI receives the validation letter, then site specific approvals should be progressed. This is done by the transferring the SSI Form electronically to the PI’s at each site who then complete, locks and signs it before sending it to the corresponding NHS R&D department for assessment. The PI should retain a copy of the signed form for inclusion in the TMF and ISF.

5.6 Applying for R&D Approval

All applications for R&D approval from NHS organisations (or from health and social care organisations in Northern Ireland) are made using the Integrated Research Application System (IRAS). Applications should be made to each relevant NHS organisation.

In Wales, submission is through NISCHR Permissions Co-ordinating Unit, who will co-ordinate the process of gaining permissions from NHS organisations in Wales.

See https://www.wales.nhs.uk/sites3/page.cfm?orgid=952&pid=52006

Each nation of the UK has a co-ordinated permission system. Wales has an agreement with the other UK nations to share the NHS R&D Form application package where they are identified as a participating nation in the NHS R&D Form. Once the application package has been shared, each nation will contact the Chief Investigator to discuss arrangements for the review of the application in their nation.

Further details can be found at:
- Scotland: NRS Permission Coordinating Centre www.NRSPCC.org
- Northern Ireland: HSC R&D Application Gateway Email: research.gateway@hscni.net

The NHS R&D Form (Site-Specific Information Form (SSI Form)) on IRAS is used to apply both for Site Specific Assessments and R&D approval at NHS sites.


For non-NHS research sites, the REC undertaking the review of the main application will undertake the SSA(s) for non-NHS site(s), generally at the same time as the review of the main application. Alternatively, an SSA can be reviewed separately by a Sub-Committee of the REC.

See more at: http://www.hra.nhs.uk/resources/applying-for-reviews/site-specific-assessment-ssa/#sthash.xAPG6VBC.dpuf
For NHS R&D review, the signed SSI Form must be accompanied by the relevant documents as listed in the checklist. It is advisable to check with local R&D offices to determine if they have any specific requirements for applications.

5.7 Substantial amendments

Amendments to the trial are regarded as ‘substantial’ where they are likely to have a significant impact on:
• the safety or physical or mental integrity of the subjects, or
• the scientific value of the trial, or
• the conduct or management of the trial, or
• the quality or safety of any IMP used in the trial.
(see SOP 3.02 Protocol development for further information)

For CTIMPs, the trial sponsor has legal responsibility for deciding whether an amendment is substantial. Guidance is available from the European Commission:

For all other research, the Research Ethics Committee that gave a favourable opinion (the ‘main REC’) has the discretion to decide whether or not a proposed amendment is substantial and requires ethical review. CIs and sponsors should seek advice from the main REC if in doubt.
The main REC must be informed of all substantial amendments by completing a notice of substantial amendment form,
http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/

The relevant R&D offices must also be notified about substantial amendments, all the copies of the regulatory approval(s) (e.g. REC, MHRA) and all other supporting documents as submitted to REC must be sent to the co-ordinating R&D office.

For CTIMP’s:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/index.htm

Substantial amendments should not be implemented until all required approvals have been obtained.
Non-substantial amendments do not need to be notified.

5.8 Maintaining approval

In order to maintain regulatory approval, systems must be in place to ensure:

• The trial is conducted in accordance with the principles of Good Clinical Practice (GCP).
• Serious unexpected adverse reactions (SUSARs) are reported in line with the required timeframe to the MHRA (for CTIMPs) and relevant ethics committee.
• Substantial amendments are notified to the relevant bodies.
• Annual safety reports (ASR) are provided to the MHRA (for CTIMPs) and relevant ethics committee.
• Allow inspection of any trial premises by MHRA inspectors as appropriate.
• Payment of the Annual Service Fee to MHRA for CTIMP’s.
• Progress reports are submitted to REC and R&D in line with their reporting requirements.

6. Training plan for SOP implementation

Training will be carried out in accordance with NWORTH training SOP 2.01.

7. Glossary of Terms

CI Chief Investigator
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

CTA Clinical Trial Authorisation
The authorisation from the MHRA to conduct a CTIMP. No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the REC may be made in parallel.

CTIMP Clinical Trial of an Investigational Medicinal Product
Any investigation in human subjects, other than a non-interventional trial, intended:
  a. To discover or verify the clinical, pharmacodynamic effects of one or more medicinal products;
  b. To identify any adverse reactions to one or more such products;
  c. To study absorption, distribution, metabolism and excretion of one or more such products with object of ascertaining the safety or efficacy of those products.

EMEA European Medicines Agency
www.emea.europa.eu

EudraCT European Clinical Trial Database

GAfREC Governance Arrangements for NHS Research Ethics Committees.

GCP Good Clinical Practice
as defined by the ICH, see www.emea.europa.eu/pdfs/human/ich/013595en.pdf

ICH International Conference on Harmonisation of Technical Requirements of registration of pharmaceuticals for human use.

ISF Investigator Site File
The file in which trial documents are kept in each site in accordance with ICP GCP.

IMP Investigational Medicinal Product
A pharmaceutical form of an active substance or placebo being tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial:

a. Used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation;

b. Used for an indication not included in the summary of product characteristics under the authorisation for that product;

c. Use to gain further information about the form of that product which are relevant to the study of the product in human subjects.

**IRAS** Integrated Research Application System
A single system for applying for the permissions and approvals for health and social care / community care research in the UK.

**MHRA** Medicines and Healthcare products Regulatory Agency
MHRA (medicines) is the competent authority for the UK in relation to the EU Directive and the Clinical Trials Regulations. MHRA (Devices) is the competent authority for the UK in relation to the medical Devices Regulations 2002.

**NHS R&D** National Health Service Research & Development
The approval body for trials taking place in NHS settings.

**NRES** National Research Ethics Service
The National body supervising the RECs.

**PI** Principal Investigator
The investigator responsible for the research site where the study involves specific procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and PI will normally be the same person.

**PIAG** Patient Information Advisory Group
If research involves the use of patient-identifiable information without consent, an application to the Patient Information Advisory Group is necessary after a favourable REC opinion.

**REC** Research Ethics Committee
A committee established in any part of the UK in accordance with GAfREC.

**SSA** Site-Specific Assessment
An assessment of the suitability of the investigator, site and facilities made for any study with a Principle Investigator at each research site. The application for SSA should be made by the Principle Investigator using the Site-Specific Information (SSI) Form, which can be found on the IRAS website.

**SSIF** Site-Specific Information Form
TM       Trial Manager

TMF      Trial Master File
File kept at NWORTH for each trial containing essential documents for that trial, as defined for CTIMP in section 8 of ICH GCP
(www.emea.europa.eu/pdfs/human/ich/013595en.pdf) and following the MRC GCP guidelines for other trials
(www.mrc.ac.uk/utilities/Documentrecord/index.htm?d=MRC002416)

8. References
6. www.mhra.gov.uk

9. Referenced SOPs
NWORTH training SOP 2.01
NWORTH site setup SOP 3.03
NWORTH trial master file 3.04
NWORTH MHRA approval SOP 4.02

10. Appendices
None