Health Research Authority

HRA Approval: Assessment Criteria and Standards Document

Contents

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INTRODUCTION

This document is **intended for reference by research sponsors and other key parties engaged in supporting researchers**. It outlines the criteria against which research studies submitted for HRA Approval will be assessed and the standards that these studies will be expected to meet. **This document and the criteria and standards within it will develop over time. You are advised to refer to the current version live on the HRA website prior to making a submission for HRA Approval.**

Part A gives detail on the areas of assessment included within HRA Approval that are additional to the UK-wide study wide governance criteria.

Part B consists of a version of the UK-wide study wide governance criteria, modified as appropriate for HRA Approval.

General questions or comments relating to this document and its contents should be addressed in the first instance to hra.approvalprogramme@nhs.net. Questions relating to specific research projects should be submitted to hra.approval@nhs.net.

Please visit the HRA Approval web pages for the current document:

http://www.hra.nhs.uk/resources/hra-approval-applicant-guidance/hra-assessment-criteria-and-standards/

Section A: Areas of review in HRA assessment which are additional to the UK study wide governance criteria

Human Resources Good Practice Framework
HRA Approval will confirm, for each activity described in the HRA Schedule of Events or Industry Costing Template, whether a Letter of Access, Honorary Research Contract or neither would be appropriate were the activities to be undertaken by NHS or University staff not already holding a contractual relationship with the organisation where the activities will take place. HRA Approval will also specify the appropriate pre-engagement checks, in accordance with the Research Passport system. For clarity, the term "if in NHS facilities", used in the Algorithm of Research Activity and Pre-Engagement Checks for the purposes of specifying when a letter of access is expected for research involving staff or their data, should be taken as referring to areas within NHS premises where care is provided. Offices and other non-care areas should be regarded as business premises and letters of access will therefore not be expected for access to such locations for staff research. External researchers working under such arrangements are expected to comply with the off-site working policies and procedures of their employing organisation. Honorary Research Contracts and/or Letters of Access may not be the appropriate mechanism/s for enabling access for researchers to independent contractors (or for access by commercial staff to NHS facilities) and HRA assessment will be clear where other arrangements are appropriate.

Principal Investigator suitability
Non-commercial sponsors are expected to state whether there should be a Principal Investigator, Local Collaborator or neither at each participating organisation (by site type), through use of the Statement of Activities. Where there should be Principal Investigators and/or Local Collaborators, the sponsor should be clear as to whether these have been identified or whether they would like local assistance in identifying suitable staff. The HRA will assess the appropriateness of the sponsor position on this and detail expectations by site type in the Initial Assessment and HRA Approval letters. It is expected that there should be a Principal Investigator where locally employed staff take responsibility for research procedures. Where this is not the case but where central study staff will be present at the participating organisation to undertake research procedures, it is expected that there will be a Local Collaborator (the role of the Local Collaborator is to support practical arrangements to facilitate the presence of the research staff under Letters of Access/ Honorary Research Contracts, etc.). Where existing data is being provided for research purposes, without additional research procedures or the presence of central research team members at site, it is not expected that there will be a Principal Investigator or Local Collaborator, as the relevant clinical staff should be able to transfer the data without the additional involvement of a named Local Collaborator. Where there should be a Principal Investigator, HRA assessment will ensure that any specific training expectations of the sponsor for them and/or their team are clear.

HRA Approval will be clear that training in Good Clinical Practice (GCP) is not a general requirement.

Host organisations remain responsible for assessing the suitability of any Principal Investigator selected, in line with the general and specific training expectations outlined by the sponsor and HRA. Participating organisations are also responsible for assessing the appropriateness of any Principal Investigator selected, in terms of any possible conflict of interest and, where appropriate, supporting the sponsor to identify an alternative Investigator. By confirming the Statement of Activities and Schedule of Events (or agreeing the site agreement) the host organisation will be taken to have confirmed the suitability and appropriateness of any Principal Investigator selected.

Level of capacity and capability assessment expected of participating organisations

NHS organisations in England participating in research should assess, arrange and confirm their capacity and capability to undertake a study, as appropriate to the nature of the study and their specific roles and responsibilities within it.

Confirmation that arrangements are in place to deliver non-commercial research should be given by agreement to the content of the Statement of Activities and Schedule of Events, for non-clinical trials.

For all clinical trials and clinical investigations (including CTIMPs, device studies, etc.), it is expected that a signed agreement between sponsor and host organisation be in place before the research commences at site. The HRA expects such agreements to be based upon a standard template (e.g. mCTA, mNCA, etc.), where applicable.

Organisations may use the Statement of Activities to confirm a specific future date on which the research may commence locally, e.g. when it is known that capability will be in place or when another study / other studies have closed (although it is not expected that such dates will be significantly in the future, as this increases the possibility of changes in circumstance that mean the study cannot be delivered as agreed).

Non-commercial sponsors should use the Statement of Activities to detail any specific capacities and capabilities that they are looking for in specific site types. The HRA will assess the requirements of the study and its site-types as part of its initial assessment and provide its guidance on whether it expects participating organisations to confirm their capacity and capability to the sponsor before the study starts at site, or whether it might be acceptable for the sponsor to assume confirmation under certain circumstances, if it does not hear to the contrary.

The following table provides an example of some scenarios and considerations involved in determining when and what level of assessing, arranging and confirming may be expected. The table is not intended to be exhaustive and sponsors may choose to contact the HRA for advice in advance of submitting their application. The Initial Assessment letter will formally clarify whether formal confirmation of capacity and capability is expected by host organisations (by site type), the likely extent of any assessment and key considerations for arranging capacity and capability.

Study / Site type Description	Assess?	Arrange?	Confirm?
Questionnaire study sent to NHS staff as participants	No	No	No. Host Organisations will be informed of the study but it may commence once HRA Approval is in place.
External researcher conducting a focus group with staff as participants	Little assess (e.g. "do we have the right staff members for the study at this organisation?")	Small arrange (e.g. book room, ensure relevant staff participants are aware)	Organisations will be informed and given 35 days to object (if for example they do not have eligible staff to participate) but study may commence without institutional confirmation if not forthcoming
Emergency Public Health Research	Assess arrangements can be made	Yes	Organisations will be informed and given specific time to object (which may be fewer than 35 days)
Continuing Care – where it is known where continuing care organisations will be up front	Yes – organisations that know they are to participate in a study 'up front' should work with sponsor to assess arrangements.	Yes – arrangements for participation should be made on the basis of the assessment.	Yes – formal confirmation that capacity and capability are in place locally to deliver the study is expected (e.g. confirmation based on statement of activities, execution of model agreement, etc.)
Continuing Care –where it is not possible to know up front which care organisations will be participating (e.g. patients treated in a HASU or NICU being transferred to their 'home' hospital).	No – for well-designed studies of this type capacity and capability expectations should not differ significantly from what is already be in place.	No – for well-designed studies of this type capacity and capability expectations should not differ significantly from what is already be in place.	Organisations will be informed and given 35 days to object (if for example they have been misidentified as the type of organisation to which the relevant patient transfers might occur) but study may commence without institutional confirmation if not forthcoming
No change to local activity but automated data extraction by central team	No	No	No. Host Organisations will be informed of the study but it may commence once HRA Approval is in place.
Activity at participating organisation limited to transfer of existing data by clinicians without consent, under s251 approval, e.g. for rare disease patients	No – organisations will not know whether or not they have an eligible participant until one is identified through	No – clinicians are expected to provide the necessary information relating to occasional rare disease cases from existing records as part of their clinical	No. The study may commence locally once HRA Approval is in place, and after the host organisation has been informed that an eligible patient record has been

identified through regular surveillance systems	surveillance questionnaires	duties	identified.
Rare genetic disease study under the UK Rare Genetic Disease Research Consortium Agreement (Musketeers Memorandum). N.B. HRA Statements of Activities completed for these studies should clearly state that the study is covered under the Consortium Agreement.	No. Studies covered by the consortium agreement are within the capacity and capability of consortium member Trusts.	No. Studies covered by the consortium agreement are within the capacity and capability of consortium member Trusts.	No. The study may commence locally once HRA Approval is in place and in line with the timelines set out in the consortium agreement.

Intellectual property
The HRA expects applicants to be clear whether their study could potentially lead to the generation of intellectual property rights (IPR). Where new IPR could potentially be generated, the HRA expects clarity from the applicant on how these IPR have/will be protected.

Section B: UK Study-wide governance criteria, as adapted for HRA Approval

1. Application Package

The Integrated Research Application System (IRAS) is the single system for applying for the permissions and approval for health and social care/ community research in the UK.

1.1 IRAS application completed correctly

Considerations	Source
Introduction The completion of the project filter tailors the application information for the type of research study, by enabling only those questions and sections that are relevant to the study. The accurate completion of the IRAS project filter is crucial to each study application. The integrated dataset for the study will be created from the answers given to the questions in the IRAS project filter. The system will generate only those questions and sections that (a) apply to the study type and (b) are relevant for the bodies reviewing the study. In addition, certain questions are enabled in response to questions in the form itself. Upon submission to the HRA, the application will be validated for REC review. Valid applications will proceed to REC review. In addition, an initial assessment will be undertaken to triage the application for HRA assessment purposes. All research studies to be undertaken within one or more NHS organisation in England should apply for HRA Approval (single-site student research that does not require an NHS REC opinion may optionally apply). As part of the triage, HRA will confirm whether the application meets the criteria for HRA Approval. Studies that meet the criteria but that have incorrectly completed project filters will be asked to submit a corrected IRAS form if the error has a material effect on the content of the application. Studies that do not meet the criteria will be given appropriate advice on applying through alternative systems. Particular attention will be given to whether an application is correctly described as a research study as opposed to	IRAS Project Filter questions as part of the IRAS application Research protocol or project proposal Participant information sheet Part C of the IRAS application

audit, service evaluation or a data or tissue bank (which are not eligible for HRA Approval).

Study-wide Considerations

Consider the study as a whole, using the study information provided by the applicant

- Have the IRAS project filter questions been answered correctly?
- Is the project research? The HRA decision tool (www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/) is available for sponsor organisations to inform their decision making process.
- If a multi-centre study, have the correct nations been identified, and are sites listed in Part C?
- Have any NHS organisations been correctly identified as Participant Identification Centres (PICs), and detailed in Part C?

When reviewing the IRAS project filter, particular care should be taken where studies involve:

a) Ionising radiation, and specifically research exposures.
   Procedures involving ionising radiation include:
   i. Diagnostic X-rays, CT scans or DXA scans;
   ii. Radiotherapy (including brachytherapy and therapy using unsealed sources; or
   iii. Radionuclide imaging (including diagnostic imaging and in vivo measurements)
   Magnetic Resonance Imaging or ultrasound investigations do not involve ionising radiation

b) Human tissue samples
   i. New tissue samples are those where the research will involve collecting samples from participants primarily for research purposes.
   ii. Existing tissue samples are those where the research will involve the use of residual material left over from routine clinical or diagnostic procedures, or existing stored samples from an archived collection or tissue bank.

c) Participants who are children
Research studies with participants who are under 16 years of age are considered to have children as participants. This also includes the use of samples or data from participants who are under 16 years of age.

d) Participants who are adults lacking capacity to consent for themselves
This includes research studies where the research could *at any stage* include adults (aged 16 and over) who are unable to consent for themselves due to physical or mental incapacity (including temporary incapacity). Particular care should be given to the potential for the research study to include further research procedures on or in relation to such participants (including collection of new samples or data) following loss of capacity to consent during the study. In Scotland consent given before the loss of capacity endures after the loss.

e) Students undertaking research as part of an educational qualification
An educational project means any research study undertaken for the purposes of an academic award. This includes doctoral research. If the research study is undertaken as part of a PhD or other doctorate the student should normally be named as the Chief Investigator. (N.B. In the case of a clinical trial of an investigational medicinal product, the Chief Investigator must be an authorised health care professional as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. This can be a doctor, a dentist a nurse or a pharmacist; each role is defined in the regulations. For a study involving significant clinical risk (other than a CTIMP), it may be appropriate to expect that the Chief Investigator is medically qualified).
If the research study is undertaken as part of an undergraduate or Masters level award the student should complete the application, but should generally not be named as the Chief Investigator. Normally the student's academic supervisor should be named as the Chief Investigator.
Students conducting research in the NHS should have on-site supervision from NHS staff (including honorary).
In Northern Ireland students, including PhD students cannot act as the Chief Investigator; this can only be undertaken by the academic supervisor.
It is expected that the following types of student studies obtain HRA Approval before commencing at any NHS organisation in England:

- study led from England which requires (or is otherwise expected under GAfREC to obtain) review by an NHS REC;
- study taking place across more than one NHS organisation;
- study that is applying for support from the NIHR Clinical Research Network (CRN).

For student studies which are taking place at a single NHS site 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. There are therefore two options for HRA Approval, depending on existing local arrangements, for single site student studies which do not require, or are not otherwise expected to obtain, NHS REC review under GAfREC:

i. Where Universities and NHS organisations currently do not require an NHS R&D form to be submitted to the R&D office but have alternative arrangements in place these should continue until 1 September 2016.
ii. 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 Statement of Activities and template Schedule of Events will not be required as there is not likely to be the need to attribute funding. Where student studies do not meet HRA assessment standards and criteria, HRA Approval will not be issued. The HRA will not "hand hold" student projects.

These arrangements will be in place until at least September 2016 by which time it is anticipated that HRA Approval will be expected for all student activity taking place in the NHS. HRA policy will be finalised following the outcome of the consultation on the UK wide policy framework.

Universities and colleges should accept the role of sponsor for all educational research conducted by their own students, unless the student is employed by a health or social care provider that prefers to do this. Sponsors of educational research should ensure that their supervisors can and do carry out the activities involved in fulfilling this role.

There is further information on applications for student studies at http://www.hra.nhs.uk/resources/before-

you-apply/types-of-study/student-research/ and for a report on the handling of student studies in the NHS see http://www.hra.nhs.uk/about-the-hra/our-plans-and-projects/replacing-research-governance-framework/educational-research/ **Notes / Resources** Help - Reference - Collated Guidance - Project Filter in IRAS List of materials considered to be 'relevant materials' under the Human Tissue Act 2004 http://www.hta.gov.uk/_db/_documents/List_of_materials_considered_to_be_relevant_material_under_the_Human Tissue_Act_2004.pdf The Medicines for Human Use (Clinical Trials) Regulations 2004. http://www.legislation.gov.uk/uksi/2004/1031/contents/made	

2. Risk to participants

NHS organisations should ensure potential participants receive accurate information on any research that they may be approached to take part in, and have a duty for ensuring any legislation relating to that research is followed thereby mitigating any risk to those participants. HRA Approval provides assurances to NHS organisations in England that information relating to a study is accurate and that the study, as described in the application document set, is compliant with legislation relating to the research.

2.1 Participant information / consent documents and consent process

Considerations	Source
Introduction Potential participants in any study need information upon which to base their decision to take part or not. Sponsors are strongly advised to make use of the Research Ethics Service Participant information sheet and consent	Research protocol or project proposal

form guidance available at http://www.hra-decisiontools.org.uk/consent/docs/PIS-Template_version1.pdf in the preparation of their participant information and consent documentation. Participant information sheets and consent forms are only part of the information given to potential participants during the informed consent process. The process of seeking informed consent may also involve a discussion between members of the research team and the potential participant. The potential participant may also have discussions with an independent person e.g. family member or GP. Where Participant Identifications Centres are to be used there should be a clear process for providing information to potential participants and this information should be clear on who is responsible for the consent process. Research ethics committees consider the ethical implications of the information provided to potential participants, and of the consent process, where relevant. NHS organisations need to be assured that potential participants receive accurate information on the research and that any legislation relating to that research is followed. HRA Approval provides NHS organisations in England with assurance that the documentation prepared for potential participants gives accurate information on the research and that the documentation and activities described are in line with any legislation relating to that research. For studies that involve only NHS staff or independent contractors as participants and that are not expected to obtain HRA REC review (see GAfREC, section 2.3.13), sponsors are expected to have considered any potential ethical matters relating to the involvement of staff as participants. HRA assessment will consider whether any substantive ethical questions remain. Where such questions arise, the study will be directed to seek an appropriate REC opinion. The HRA expects organisations hosting research to accept these assurances as to the ethical acceptability of the research. Common law duty of confidentiality applies to all staff-only studies (section 251 does not apply to staff-only studies, as section 251 relates explicitly to medical records). **Study-wide considerations** • Consider the proposed consent process to ensure that any legal implications presented by the study are addressed. Any specific expectations within the participant information sheet and consent process that may	Participant consent form Participant information sheet Advertisement materials for research participants Letter of invitation to participant NHS REC favourable opinion letter, when available Statement/s of Activities Schedule/s of Events

have local implications should be highlighted. • The participant information sheet should clearly describe the study, including the arrangements for potential participants' involvement, and be consistent with the other study documents (protocol, IRAS form etc.) • Consider the accuracy of the information describing which organisation is responsible for providing care to the participant. Consider the accuracy of the information relating to insurance/indemnity and compensation • Consider the accuracy of any specific expectations relating to study treatment and a participant's care after their participation in the study. • Ensure that the arrangements for care after research do not lead to expectations by participants of care that cannot be guaranteed. Where specific arrangements for post-study care are described, the sponsor must specifically describe the arrangements for provision. • The full study title and IRAS reference should be present on both the participant information sheet/s and informed consent form/s, except in circumstances where inclusion of the full study title would not be appropriate. This is in order that participants have a single reference for a study. • The participant information sheet must be clear about how participant data will be used, who it will be shared with, how and when (including clarity on how security and integrity will be ensured) and what will happen to it, including after the study. • The participant information sheet must be clear about how human biological material (including Relevant Material for the purposes of the Human Tissue Act) will be used, who it will be shared with, how and when (including clarity on how security and integrity will be ensured) and what will happen to it, including after the study. • It is not expected that the consent form has a clause for every activity, on the proviso that participant activity is clear in the PIS. However, if participants' personal identifiable data is leaving the European Economic Area (i.e. the EU member states, as well as Iceland, Lichtenstein and Norway), this must be clear in the participant information sheet and a specific consent clause for this must be present in the informed consent form.	

• The participant information should give a point of contact for queries and/or complaints. This may be a place holder for insertion of local details or, where appropriate, this may be a central contact (or a combination of the two). The sponsor may allow localisation of the PIS and ICF in a variety of ways including printing on headed paper, use of a sticker or other clearly identified mechanism. • The informed consent form, where needed, should provide places for signatures of both an appropriate member of the research team and the participant, except in circumstances where consent is being returned by post or electronically and where countersignature by the researcher may not be appropriate. • It should be clear to research staff taking consent that an original copy of the participant information sheet and completed informed consent form is to be given to the participant, in addition to the original copy that is filed in the investigator file. • Consent may be implied where appropriate, for example through the return of a questionnaire. • It should be clear to participating organisations from the study documentation who (e.g. staff type, member of normal clinical team, etc.) will be allowed to identify potential participants and make the first approach about the study (be this external staff associated with the sponsor or local research team members). It should be clear who will access identifiable information in order to identify potential participants and the basis in law for this should be justified. • Where children are to be included as participants, arrangements for taking consent and, where appropriate, assent should be clear in the protocol and the different information, consent and assent documentation should be clearly labelled for use. It should also be clear (where applicable) what arrangements will be in place for obtaining consent from participants assented as children upon attaining majority, should they do so whilst still participating in the research. • Where Participant Identification Centres are to be used there should be a clear process for providing information to potential participants. It should be clear who is responsible for which aspects of the process. This should include clarity for the potential participant on under whose care they would be for the purpose of the study (i.e. the research site, not the PIC).	

• For clinical trials, the participant information sheet should include a short description of the drug, device or procedure being tested and describe the stage of its development. The potential side effects of these interventions should be clearly set out in the participant information sheet. • Some pragmatic trials may compare two or more medications which are standard of care for patients with the condition being investigated, and participants (or centres) are randomised to receive one of the standard care medications. Where this is the case, it is acceptable for the participant information sheet to simply state that the side effects are described in the information leaflet which comes with the medicine (or similar). **Notes / Resources** http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/	

3. Risk to study

The study sponsor is ultimately responsible for the study design however NHS organisations are responsible for reviewing protocols to ensure risks to the study are addressed through the study management arrangements. HRA Approval will provide assurance that the study documents describe the study in a clear, consistent and accurate fashion. Where particular arrangements are expected of participating organisations, HRA Approval (through the Initial Assessment Complete and HRA Approval letters) will describe these.

3.1 Protocol assessment

Considerations	Source
Introduction The protocol should describe the objectives, design, methodology, statistical considerations (or other methods of data analysis) and the organisation of the study. It is recommended that a protocol describes the monitoring of the study and dissemination of the study findings. The content of a protocol may vary depending on study type but all protocols should provide a clear description of the study activities, to ensure that the study may be conducted as intended in a consistent and repeatable fashion. A study must follow the protocol agreed by the study sponsor and approved by the relevant regulatory bodies. It is the Sponsor's responsibility to ensure the study has scientific review that is proportionate to the study type, although RECs have the right to review the appropriateness of the scientific critique/peer review that is presented to them. HRA assessment will check that the protocol maintains consistency with the other study documents to accurately and consistently describe the study. For non-commercial studies, this includes the description of study arrangements at the organisational level (including, where relevant, at different site types) in the Statement/s of Activities and the Schedule/s of Events. In future, HRA assessment may include checks that specific templates have been used, or specific standards followed (see CTIMP protocol template and qualitative protocol template for background). **Study-wide considerations** ▪ Confirm the conduct and management of the study at the NHS research site(s) has been described in the protocol	Research protocol or project proposal Participant information sheet IRAS Form Statement/s of Activities Schedule/s of Events

4. Risk to organisation

A complex array of organisations and individuals may be involved in a study. There should be appropriate clear agreement of the allocation of responsibilities and rights. HRA Approval will provide clarity to the NHS on the agreement/s intended for use by the sponsor.

4.1 Allocation of responsibilities and rights are agreed and documented

Considerations	Source
Introduction NHS Organisations in England are expected to confirm their readiness to commence their participation in a HRA Approved research study through the act of agreeing the content of a document ("agreement") with the study sponsor. The HRA Initial Assessment Complete Letter (and HRA Approval letter) will specify the appropriate agreement for each site type in a study. The document might be the Statement of Activities and Schedule of Events, an unmodified model agreement (e.g. mCTA) or another document provided by the sponsor. All non-commercially sponsored applications should be accompanied by a completed Statement of Activities and Schedule of Events, which details the activities to be undertaken locally and whether these will be undertaken by local or central study staff. For studies where activities will differ at different host organisations (i.e. where there is more than one site type in the study) one Statement of Activities and Schedule of Events should be provided per site type (N.B. – this is not the same as one per site. Additional Statements should only be provided per 'site type', when research activities differ between these site types). HRA assessment will review the consistency of activities described in the Statement of Activities with the description within the protocol, participant information sheet, etc. For non-commercial studies other than clinical trials, the HRA strongly encourages use of the Statement of Activities and Schedule of Events by sponsors to formally record the agreed activities to be undertaken at each participating organisation and their associated responsibilities, in place of any other form of agreement. However, it is accepted that the Statement of Activities is a document still undergoing user testing. Where the sponsor elects to use its own template for agreement with sites, the HRA expects that the Statement of Activities and Schedule of Events will still be completed and supplied as part of the application, alongside any additional template agreement that the sponsor	Research protocol or project proposal Contract / study agreement Statement/s of Activities Schedule/s of Events

intends to use with participating organisations.

Where it is expected that there be an agreement between sponsor and site (including all commercially sponsored studies), it is strongly recommended that an unmodified model agreement is used. These agreements should be used as set out in their accompanying guidance. Where a template based on the model agreement is submitted but includes modification, the sponsor will be asked to explain the rationale for such modification. Currently, this explanation will be for the information of participating organisations, i.e. the HRA will not provide an opinion on the validity of such justification. Where template model agreements are not available the sponsor, under the research governance framework, is responsible for providing template study-specific agreements for the organisations responsible for the research sites. Where an agreement not based upon a model template is used, the sponsor will be asked to explain the rationale for not using a model agreement. Currently, this explanation will be for the information of participating organisations, i.e. the HRA will not provide an opinion on the validity of such justification.

When working in [Country] with...	England	Scotland	Wales	Northern Ireland
Model agreements	The UKCRC model agreements have been negotiated with English law and governance arrangements at their core.	Use versions modified for use under the legal systems and administrative arrangements of Scotland.	Use versions modified for use under the legal systems and administrative arrangements of Wales.	Use versions modified for use under the legal systems and administrative arrangements of Northern Ireland.

Study-wide considerations

- Confirm if a template agreement is to be used for the study or whether any modifications in the template have been made.
- Confirm if the template agreement is a model agreement, a modified model agreement or where no model agreement is available ensure the sponsor provides a template study-specific agreement for the organisations responsible for the research sites, if appropriate
- Although not legally required it is recommended to use a material transfer agreement for the transfer of

tissues, as being compliant with Human Tissue Act(s). This may be embodied within the Contract/ Study Agreement or a separate Material Transfer Agreement. Where a separate agreement is to be used obtain a copy of the template and justification from the sponsor for not using the material transfer clauses in the Statement of Activities. ▪ Provide clarification on the form of the agreement between the sponsor and NHS Research sites. ▪ For non-commercial studies the application for HRA Approval should include the template or templates of the agreement/s that the sponsor intends to use for agreement with its participating organisations, as well as one Statement of Activities and one Schedule of Events completed per 'site type'. This is unless the sponsor intends to use the statement and schedule as the form of agreement, in which case there is no expectation that additional template agreements are submitted. Generally speaking, the HRA would expect template agreements in addition to the Statement of Activities for clinical trials. **Notes / Resources** Model commercial and collaborative agreements http://www.crncc.nihr.ac.uk/Life+sciences+industry/Set-up/agreements.htm Model agreements http://www.ukcrc.org/regulationgovernance/modelagreements/ An agreement would normally specify: ▪ The sponsor organisation for the study ▪ The distribution of the key responsibilities And, where appropriate: ▪ The arrangements for financial management with reference to criteria 4.3 ▪ The arrangements for monitoring of the study, pharmacovigilance or safety reporting ▪ The level of compensation for negligent and non-negligent (for commercial studies or if specified by the REC) harm ▪ Any services contracted out to a third party (e.g. central laboratory services; centralised ECG interpretation; study monitoring and data collection).	

Some of the information may be contained in other documents.	

4.2 Insurance / indemnity arrangements assessed

It is a sponsor's responsibility to ensure there is provision for indemnity or compensation in the event of injury or death attributable to a study, and any insurance or indemnity to cover the liability of the investigator and sponsor(s).

Considerations	Source
Introduction The application for HRA Approval should make clear the insurance and indemnity arrangements that are to be in place for the management, design and conduct of the study. The application should detail if more than one organisation is responsible for such arrangements and it should also be clear whether this is through NHS or other arrangements. A copy of the relevant (non-NHS) policy or policies should be provided, or if not available then a copy of the insurance certificate/s and confirmation from the Sponsor that there are no applicable exclusions that would affect the insurance cover available for study participants. It is expected that NHS organisations do not request renewals of insurance certificates since it is the sponsor's responsibility to maintain insurance as set out to the REC. Any change to the insurance arrangements would constitute a substantial amendment. <u>Insurance Arrangements</u> The insurance arrangements should be relevant to the study. The insurance should cover the inclusion criteria of eligible participants, including participants of child bearing potential and participants who are breast-feeding where applicable. A copy of the insurance certificate is expected for all studies sponsored other than by NHS organisations. The expiry	Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only) Contract / study agreement Participant Information Sheet

date should be at least one month after the application for HRA Approval has been submitted. It should be clear within the application whether the insurance limit is capped for the study as a whole or per patient. The HRA will request a justification from any sponsor of a clinical trial not providing £5M of insurance cover. *Studies recruiting NHS staff only* For studies limited to recruiting NHS staff and/or independent contractors as participants and not requiring REC review, proof of insurance/indemnity for the design/management of a study will not be requested. However, where the organisation responsible for the design of the study (e.g. the employer of the CI) is not the research sponsor, a separate statement (email) from the organisation responsible for the study design should be provided evidencing that they are aware of their responsibilities and vicarious liabilities. *Negligent harm indemnity:* The policy/ insurance certificate shall usually specify Public & Products liability (including Clinical Trials Liability, where relevant) and Professional/ Employers liability. ***Management of the study:*** The sponsor will normally hold insurance or provide indemnity to cover their liabilities as sponsor which would cover the overall management of the study. For ***commercial studies*** where a company is sponsor then insurance will be provided through an insurance scheme. A copy of the relevant policy/ certificate should be provided, where not included within the contract/study agreement. For ***non-commercial studies*** where a university or higher education institution is sponsor then insurance will be provided through an insurance scheme. A copy of the relevant policy/ certificate should be provided. Where an NHS organisation is a sponsor, then indemnity is provided through NHS schemes. No proof of indemnity is expected for NHS sponsored research. If a NHS member of staff performs research activities in a non-NHS location then NHS	

indemnity still applies. ***Design of the study:*** The design of the research is the responsibility of the protocol author, unless this responsibility has been assumed by the sponsor (where different from the author) and normally the employer of the author will hold insurance or provide indemnity to cover their liabilities. For ***commercial studies*** the insurance will be provided through an insurance scheme. A copy of the relevant policy/ certificate must be provided, where not included within the contract/study agreement. For ***non-commercial studies*** where the protocol author is employed by a university or higher education institution, or the design of the research has been undertaken in the course of an honorary arrangement with a university or higher education institution then insurance will be provided through an insurance scheme. A copy of the relevant policy/ certificate should be provided. This situation applies to researchers employed by a university, regardless of whether or not they hold any honorary contract with an NHS organisation. For ***non-commercial studies*** where the protocol author is the substantive employee of an NHS organisation, then indemnity is provided for harm arising from the design of the study through NHS schemes. No proof of indemnity is expected. However, where an NHS organisation is responsible for the design of the study (e.g. the employer of the CI) but is not the research sponsor, a separate statement (email) from the organisation responsible for the study design should be provided evidencing that they are aware of their responsibilities and vicarious liabilities. ***Conduct of the study:*** The conduct of the research refers to the study procedures, as described in the protocol or proposal, which are conducted by the research team with participants, data or tissues. Employers of the research team are normally responsible for the actions of their staff who conduct research procedures as part of their employment. A study may be of differential risk to different NHS Organisations depending upon their role in the study. Where the research involves NHS patients under the care of NHS organisations, indemnity for harm to participants	

resulting from clinical negligence is provided through NHS indemnity schemes. No proof of indemnity is expected. ***Primary Care:*** Independent contractors (e.g. GP practices, NHS dental practices) or the staff members they employ are not normally covered by NHS indemnity. Where the research involved NHS patients under the care of independent contractors, indemnity for harm to participants resulting from clinical negligence is provided through professional indemnity. Independent contractors are usually covered for clinical negligence through Medical Defence organisations or similar bodies. The cover provided is normally for the services they are providing to the NHS under contract. Independent contractors should ensure that they are covered to undertake research activity through this cover or through separate arrangements. *Non-negligent harm indemnity (also known as No Fault compensation):* For ***commercial studies,*** arrangements for no fault compensation will normally be provided in accordance with the Association of British Pharmaceutical Industry (ABPI) or Association of British Healthcare Industry (ABHI) schemes. A copy of the form of indemnity (unsigned) to be used should be included in the model agreement. Any ABPI member who is not providing 'no fault compensation' in accordance with the ABPI standards will be asked to provide a justification. Non-ABPI members will be asked if they are aligned with this policy and, if not, to provide justification. For ***non-commercial studies,*** arrangements for no fault compensation cannot be made in advance by the NHS or other public bodies (e.g. MRC). Such organisations, although not accepting liability, may consider making an ex gratia payment on a voluntary basis in the event of a claim. It is the role of RECs to decide whether or not a study can go ahead without a scheme of compensation for harm caused where there is no negligence. For ***non-commercial studies,*** some universities or higher education institutions may choose to provide no fault compensation for research involving their employees. If this is the case a copy of the policy should be provided. *Equipment indemnity:* Occasionally a research site might not have access to a piece of specific equipment to undertake the study, e.g. an	

ECG machine that transmits data directly to a central reading facility. In this case the Sponsor might make arrangements for the piece of equipment to be loaned or gifted to the research site. The equipment might be provided to all sites or to individual sites. Although it might be arranged by the Sponsor, the supplier of the equipment is not usually the Sponsor. **Study-wide considerations** Before a study is initiated an agreement about compensation in the event of harm to participants should have been reached. If any organisation, or the sponsor themselves, offers compensation without proof of negligence, they should have made the appropriate arrangements. Review the following aspects of the insurance/ indemnity arrangements: ▪ Assess whether there should be an insurance certificate / policy (not expected for studies where NHS indemnity covers the liability that arises from the management, design or conduct of the study) ▪ The level of insurance/ indemnity and if it is appropriate to the study type and purpose ▪ Any specific exclusions to the cover provided ▪ If the study is being conducted by independent contractors (e.g. GP practices, NHS dental practices) For studies where study specific equipment is to be loaned or gifted to a research site confirm what equipment is to be loaned or gifted. HRA Approval will clarify the planned arrangements for equipment that is to be loaned or gifted (e.g. registration with the Master Indemnity Scheme) and ensure that this clarity is presented within the HRA Approval letter and, where possible, the Initial Assessment letter. There is no master indemnity agreement scheme in place for Northern Ireland. Equipment indemnity is covered and managed as part of each HSC Trust "Policy for the Management of Medical Devices", which has an indemnity form to be completed by suppliers of all equipment on loan or gifted to HSC Trusts. **Notes / Resources** The Medicines for Human Use (Clinical Trials) Regulations 2004 – SI 2004/1031 http://www.legislation.gov.uk/uksi/2004/1031/contents/made The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 – SI 2006/1928, Schedule 1, Part 2, (14)	

http://www.legislation.gov.uk/uksi/2006/1928/contents/made Responsibilities, liabilities and risk management in clinical trials of medicines http://www.ct-toolkit.ac.uk Arrangements for Clinical Negligence Claims in the NHS http://www.nhsla.com/claims/pages/clinical.aspx Association of the British Pharmaceutical Industry (ABPI) Indemnity Form http://www.abpi.org.uk/our-work/library/guidelines/Pages/indemnity-england-wales.aspx (England and Wales) http://www.abpi.org.uk/our-work/library/guidelines/Pages/indemnity-scotland.aspx (Scotland) Association of British Healthcare Industries (ABHI) Indemnity Form http://www.abhi.org.uk/key-issues/technical-regulatory/Clinical-Investigations.aspx Equipment Indemnity England: http://nhsmia.bipsolutions.com/ Scotland: http://www.hfs.scot.nhs.uk/online-services/master-indemnity-agreement/ Wales: http://www.whs.wales.nhs.uk/supply/masterindemnity Ireland: HSC R&D Office contact details can be obtained from www.publichealth.hscni.net/directorate-public-health/hsc-research-and-development	

4.3 Financial arrangements assessed

The way in which a study is financed is important to NHS organisations as they are legally accountable for use of public funds in compliance with the law and the rules set out by HM Treasury.

Considerations	Source
Introduction It is important that NHS organisations are aware of the activity involved in supporting a study and what it costs. NHS	Letter from funder (if applicable)

organisations should be aware of the planned expenditure and attribution of costs to ensure financial probity, compliance with the law and with the rules set out by HM Treasury regarding the use of public funds. Where the study is funded through one or more programme grant(s), the IRAS application should reflect the amount or percentage of funding that is to be used for the study. This will give a clearer indication of the study funding than the value of the total programme grant. For non-commercially sponsored studies, the Statement of Activities is intended to contain a description of what funding (if any) is to be provided to each site type in England to cover research costs. It also requests that the sponsor specifies what support (e.g. for activities incurring under service support costs) should be in place locally to deliver the study. Although the Schedule of Events is designed for sponsors to attribute the site costs of their research, the HRA will not currently provide a judgement on adequacy of funding or appropriateness of cost attribution. It is intended that this assurance will be added to HRA Approval once the Statement of Activities and Schedule of Events have undergone further testing in use. For commercially sponsored studies, the submission to the HRA should include a completed NIHR industry costing template (validated by the lead local clinical research network where it is intended that the study will be included on the NIHR portfolio, see http://www.crn.nihr.ac.uk/can-help/life-sciences-industry/ for details). For studies not intended to be included on the NIHR Portfolio, the submitted NIHR Industry Costing Template will undergo validation within the HRA. Sponsors should be aware that validation of an Industry Costing Template within the HRA is likely to take more time than accepting a pre-validated template. **Study-wide considerations:** **Non-Commercial Studies** ▪ Ensure the letter from funder is received (if applicable) ▪ Consider whether the financial management arrangements have been appropriately described. ▪ Consider the appropriateness of arrangements to reimburse other parties. ▪ Ensure that the activities described in the HRA Schedule of Events are consistent with other study	Costing template, or equivalent Contract / study agreement Cost attribution template (where used) or Statement/s of Activities and Schedule/s of Events (England)

documentation, e.g. protocol and participant information sheet. **Commercial Studies:** • The NIHR Industry Costing template should be completed and submitted with the application. Where the study is intended for the NIHR CRN portfolio, the template should have been validated in advance by the lead network. Where the study is not intended for the CRN portfolio, validation will occur within the HRA. **Post-Study Arrangements** • Participants should not be given false or unrealistic expectations of post-study access to the study intervention. Where the application (particularly the participant information) suggests that post-study access to study therapies will be afforded to participants, the HRA will expect the sponsor to provide evidence as to how this access will be funded and arranged. In Scotland Please follow the relevant NRS guidance for Determining a Price for Commercial Research Studies across Scotland and the relevant process for non-commercial costings and detail in National Differences section of Study-Wide Governance Report if applicable. **Notes / Resources** Attributing the costs of health & social care Research & Development (AcoRD) http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_133882 NIHR Industry Costing Templates http://www.crncc.nihr.ac.uk/Life+sciences+industry/Set-up/costing.htm	

5. Legal Compliance

5.1 Compliance with the Data Protection Act and data security issues assessed

Considerations	Source
Introduction The NHS treats the largest pool of patients in the world, providing services from a person's birth to their death. The NHS therefore is a vast source of patient data. The use of a patient's data is covered by a large range of legal and professional obligations. There are also a number of statutes that describe how a patient's data may be disclosed and used. NHS organisations are required to protect the way identifiable data is handled in accordance with the Data Protection Act 1998, ensure privacy is maintained in accordance with the Human Rights Act 1998 and satisfy the obligation of confidentiality in common law. Under common law all research using identifiable patient data requires the express (explicit) consent of the patients involved or another legal basis. In certain circumstances, and with the necessary approvals, the common law duty of confidentiality may be set aside so that information that identifies patients can be used without their consent. It should be noted that an assurance of maintaining confidentiality by someone receiving identifiable data does not provide a basis for access unless the access is given with consent or another legal basis. The NHS has a number of codes of practice regarding information governance that should be followed in relation to the disclosure and use of patient's data. These include: ▪ Confidentiality: NHS Code of Practice ▪ Information Security Management: NHS Code of Practice ▪ Records Management: NHS Code of Practice ▪ NHS Information Governance – Guidance on Legal and Professional Obligations	IRAS questions on data Contract / study agreement (data access agreements)

Any research study involving identifiable NHS patient data should abide by the responsibilities set out in the Research Governance Framework. Researchers have to gain NHS REC favourable opinion for their study[1], obtain informed consent from participants, or Section 251 support (where applicable), and meet the requirements of the Data Protection Act. The Data Protection Act states that information should be available to patients that makes them aware of the potential uses of their data. The Organisation where the data collected will reside may be, or may host, an Accredited Safe Haven. In England and Wales these are regulated under section 251 of the NHS Act 2006 and allows for the processing of data that might be personally identifiable in a controlled environment. **Study-wide considerations** The Sponsor is responsible for ensuring that the protocol and study-wide management arrangements comply with the law. Sponsors may, however, not be familiar with NHS-specific standards or codes. Consider the use of patient data to identify and approach potential participants as well as the consent, confidentiality and security of the disclosure and use of a participant's data in the study. This includes the means for exercise of data subjects' rights, including rights of access, and objection to the use of personal data, and use of data after the study. ▪ Has the disclosure and use of a participant's data been adequately described? ▪ Have the requirements of the Data Protection Act been considered? ▪ Have the measures for data security been considered? ▪ Is a safe haven being utilised, if so, please highlight on study-wide report?	

[1] Under paragraph 2.3.13 of the Governance Arrangements for Research Ethics Committees (2011) – *GAfREC* certain studies are not expected to seek an NHS REC favourable opinion.

Patient Information Sheets and Consent Under common law, informed consent must be obtained before personal data can be collected. Information should be provided on: ▪ The purposes for which the data are to be processed ▪ What data are to be collected ▪ Who the information will be disclosed to ▪ Whether any uses or disclosures are optional. Consent is not required when using anonymised[2] data *Data confidentiality and security* Research participant data needs to be maintained confidentially and securely and consideration should be given to: ▪ The flow of data between parties involved in the research study ▪ Who will access the data and what information they will be able to access and whether this is covered by consent ▪ How the data will be stored and what security measures (both physical security and electronic security) are in place to make sure the data is secure ▪ Will the data be used in an identifiable; coded or anonymised format and if it is coded or anonymised are the methods of coding or anonymisation clearly described ▪ Whether the disclosure and use of a participant's data been adequately described and justified ▪ Whether the minimum necessary participant identifiable information is being used	

[2] Data that contain personal information can be subject to different degrees of de-identification, these are:
- **Identified** – these data contain personal identifiers from which individuals can be distinguished.
- **Coded** – identifiable information is substituted by a code of randomly assigned numbers and/or letters. The data is anonymous to the research team and the key to the code is held securely by those responsible for the participants' care or a third party.
- **Anonymised** – all personal identifiers or codes are removed.

▪ Security of data whilst physically transporting, either electronic (e.g. USB) or paper Particular consideration should be given to situations where there is a risk of access to sensitive health information (i.e. mental or sexual health) through access to full medical records. Prior to participant consent only the clinical care team have the right to access patient data. *Use of identifiable data without consent* It is possible, in certain circumstances, for the common law duty of confidentiality to be set aside so that information which identifies participants can be used without their consent. In England and Wales researchers must seek approval from the Health Research Authority through the Confidentiality Advisory Group (CAG). In Scotland advice should be sought from the National Services Scotland, Privacy Advisory Committee on access to ISD data. In Northern Ireland, researchers should refer to the Privacy Advisory Committee (Northern Ireland) Code of Practice and seek advice from HSC Trust Data Guardians. Where researchers are seeking Patient Identifiable Information without consent, the information should still describe: ▪ Explicit details about data flows and who will access what identifiable information ▪ Evidence why consent is not practicable ▪ Full justification why someone external to the clinical care team should be allowed to access patient identifiable data ▪ Details of how patients and service users or representatives from relevant patient and service user organisations have been engaged and how their views influenced the methodology and whether they regard the use of patient information without consent acceptable ▪ Justification why each item of identifiable information is being requested ▪ Justification why the use of identifiable information achieves the purpose of the study The lead nation responsible for conducting the study-wide review should highlight to the other UK nations their participation in the study using identifiable data without consent. The participating nations can then assess this aspect of the study according to their own nation's processes.	

When working in [Country] with...	England	Scotland	Wales	Northern Ireland
Data without consent	Section 251 of the NHS Act 2006 applies	No equivalent to section 251 of the NHS Act 2006 Caldicott applies	Section 251 of the NHS Act 2006 applies	No equivalent to section 251 of the NHS Act 2006

Transfer of data to a country or territory outside the European Economic Area (EEA)

The eighth core principle of the Data Protection Act says that data should be transferred only to countries with adequate security. This means the transfer of personal data to a country or territory outside the EEA is prohibited *unless* that country of territory ensures an adequate level of protection for the rights and freedoms of the individuals to whom those personal data belong. The EEA consists of the member states of the European Union plus the European Free Trade Association States. HRA assessment will not make an assessment of adequacy of levels of protection in non-EEA countries or territories. The HRA will expect that, where it is planned to transfer identifiable data outside of the EEA, the possible implications of this should be clearly described in the participant information and explicitly consented to with a clause in the consent form. Information should describe the country or territory to which the personal data is being transferred.

The onus is on the applicant to describe how adequate safeguards will be put in place to protect data transferred outside of the EEA. This may include reference to Standard Contractual Clauses and Binding Corporate Rules.

The reviewer conducting the study-wide review should highlight to others that the data is being transferred outside the EEA.

Use of patient or service user records to identify potential participants

The searching of patient or service user records for potential research subjects can be done legally by fulfilling any of the following criteria: ▪ The researcher gains the explicit consent of every patient with a record in the population pool being assessed ▪ The search is conducted by a health or social care professional who has a 'legitimate relationship' with the patient, such as a clinical or social worker ▪ The search is conducted by a researcher who is part of the clinical team ▪ The search makes use of 'privacy enhancing technologies' ▪ Support under section 251 regulations is granted for the research (in England and Wales) **Notes/Resources:** Data Protection Act 1998 http://www.legislation.gov.uk/ukpga/1998/29/contents **Confidentiality: NHS Code of Practice:** England: https://www.gov.uk/government/publications/confidentiality-nhs-code-of-practice A guide to confidentiality in health and social care http://www.hscic.gov.uk/media/12822/Guide-to-confidentiality-in-health-and-social-care/pdf/HSCIC-guide-to-confidentiality.pdf A guide to confidentiality in health and social care references http://www.hscic.gov.uk/media/12823/Confidentiality-guide-References/pdf/confidentiality-guide-references.pdf Scotland: http://www.knowledge.scot.nhs.uk/media/CLT/ResourceUploads/4011563/Revised%20Code%20of%20Confidentiality%20-%20Final.pdf Wales: www.wales.nhs.uk/sites3/documents/950/codeofpractice.pdf Northern Ireland: www.dhsspsni.gov/confidentiality-code-of-practice **Information Security Management:** England, Wales and Northern Ireland: NHS Code of Practice: http://systems.hscic.gov.uk/infogov/codes/securitycode.pdf	

Scotland: http://www.scotland.gov.uk/Publications/2008/07/01082955/10 **Records Management:** England, Wales and Northern Ireland NHS Code of Practice: http://systems.hscic.gov.uk/infogov/links/recordscop1.pdf and England, Wales and Northern Ireland: http://systems.hscic.gov.uk/infogov/links/recordscop2.pdf Scotland: http://www.scotland.gov.uk/Publications/2012/01/10143104/9 **NHS Information Governance – Guidance on Legal and Professional Obligations** England, Wales and Northern Ireland: http://systems.hscic.gov.uk/infogov/codes/lglobligat.pdf England & Wales: Section 251 of NHS Act 2006 approval for the use of data without consent through the HRA Confidentiality Advisory Group http://www.hra.nhs.uk/resources/confidentiality-advisory-group/ Scotland: Approval is sought from National Services Scotland, Privacy Advisory Committee for access to ISD data. (http://www.nhsnss.org/pages/corporate/privacy_advisory_committee.php) Where access to locally held identifiable data is requested, Boards may expect that Caldicott Guardian approval is sought and obtained. Northern Ireland: Researchers should refer to the Privacy Advisory Committee (Northern Ireland) Code of Practice http://www.privacyadvisorycommittee.hscni.net/ and HSC Trust Data Guardians.	

5.2 CTIMPs – Arrangements for compliance with the Clinical Trials Regulations assessed

Considerations	Source
Introduction The conduct of clinical trials of investigational medicinal products (CTIMPs) in the UK is regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. The regulations include a number of provisions that are important to the protection of public health. ▪ **Good Clinical Practice** – The requirement to conduct all CTIMPs in accordance with the principles of good clinical practice (GCP) helps ensure that all CTIMPs conducted in the UK are to the appropriate high standard and the risks to participants are minimised. ▪ **Good Manufacturing Practice** – The requirement to manufacture all investigational medicinal products (IMPs) to good manufacturing practice (GMP) standards ensures participants do not receive poor quality or badly prepared medicines. ▪ **Inspections** – Inspections by the Medicines and Healthcare products Regulatory Agency (MHRA) to check the principles of GCP and GMP are being followed improves the overall quality of CTIMPs conducted in the UK and identifies areas of non-compliance. ▪ **Protection for incapacitated adults** – There are provisions for the additional protection of adults unable to give informed consent, who should be able to participate in a CTIMP and maybe benefit from an improved condition. ▪ **Protection for minors** – There are provisions for additional protection of minors (i.e. persons under the age of 16) who are being considered for participation in a CTIMP. ▪ **Pharmacovigilance arrangements** – Investigators and Sponsors together must record safety information and report serious unexpected adverse reactions thought to be caused by the IMP to the MHRA. When considering granting a Clinical Trial Authorisation (CTA), the MHRA assess the information and data relating to both the handling and safety of the IMP. The MHRA does not review the participant information sheet or review the	Research protocol or project proposal Contract / study agreement Statement/s of Activities template Schedule/s of Events template

arrangements for the monitoring or pharmacovigilance of the CTIMP (although a check for safety reporting provisions is conducted). When considering giving a favourable opinion, the NHS Research Ethics Committee (REC) reviews the participant information sheet and the overall arrangements for monitoring safety during the study. **Study-wide considerations** Under the regulations the Sponsor has specific responsibilities in relation to the initiation, management and financing (or arranging the financing) of a CTIMP. The Sponsor may delegate tasks within these responsibilities to third parties or to the research site. When reviewing the compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, consideration should be given to the following: ▪ Conduct of the CTIMP at the research site i. Assess whether the protocol sets out clearly the arrangements for the conduct of the CTIMP at the research site, so that research sites will understand what is expected of them. ii. Assess whether the template clinical trial agreement between the Sponsor (or their representative) and the research site, sets out clearly the arrangements for the conduct of the CTIMP at the research site. Where there is no clear description of the arrangements for the conduct of the CTIMP at the research site obtain clarification from the Chief Investigator/ Sponsor. For non-commercial clinical trials, assessment of clarity at site level will include assessment of the Statement/s of Activities and Schedule/ of Events. ▪ Delegation of activities i. Highlight those activities that the Sponsor is delegating to a third party and any expectations of the third party when working with the research site.	

ii. Highlight those activities the Sponsor is delegating to the research site and identify any specific capacities and capabilities that the research site might have to achieve to carry out the delegated activities. ▪ Participant information and consent i. Where there are differing types of participant information sheets or consent forms, is there clear guidance regarding the circumstances in which different documents should be used. ii. Consider if there is clear guidance and information relating to the consent of participants to take part in the CTIMP. If relevant, is there specific information and guidance on the consent of adults lacking capacity, ongoing consent relating to changes in the CTIMP, ongoing consent relating to the loss of capacity, arrangements for the withdrawal of participants? ▪ Management of the CTIMP at the research site i. Assess whether the arrangements for the management of the CTIMP at the research site has been clearly described especially in relation to: o Monitoring of the CTIMP at the research site and processes for source data verification; o Pharmacovigilance of the CTIMP at the research site and the processes for reporting adverse events; o Verification of the consent process and participant's consent to take part in the CTIMP; o Handling of the Investigational Medicinal Product (IMP) and the processes for its storage, preparation and dispensing; and o Maintaining security and processes for storage and archiving of trial materials such as documents and samples. ▪ Adults with Incapacity in Scotland i. Where the trial is to be conducted at one or more sites in Scotland, and the Chief Investigator is professionally based in Scotland, it should be allocated to "the Ethics Committee" constituted by Scottish Ministers under the Adults with Incapacity (Scotland) Act 2000 (Scotland A REC). If the Chief	

Investigator is based outside Scotland, the application may be allocated to any other recognised REC. Notes / Resources **Medicines for Human Use (Clinical Trials) Regulations 2004, as amended** http://www.legislation.gov.uk/uksi/2004/1031/contents/made **Annex 13, Investigational Medicinal Products, Volume 4 EU Guidelines to The Good Manufacturing Pharmacovigilance Practice Guide** http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf **EudraLex - Volume 10 Clinical trials guidelines** http://ec.europa.eu/health/documents/eudralex/vol-10/ **Clinical trials for medicines** http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm **ICH Topic E 6 (R1), Guideline for Good Clinical Practice Section 5.18 - Monitoring** http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf **Consent Guidance** http://www.hra.nhs.uk/documents/2013/09/information-sheet-and-consent-form-guidance.pdf **ICH Topic E 6 (R1), Guideline for Good Clinical Practice Section 5.14 - Supplying and Handling Investigational Product(s)** http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf **Archiving of Documents** http://www.ct-toolkit.ac.uk/routemap/archiving	

5.3 Compliance with any applicable laws or regulations

<table>
<tr><th>Considerations</th><th>Source</th></tr>
<tr><td>
Introduction
There are some key differences in research related legislation across the UK, other than the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended, which apply UK-wide.

The reviewer will be responsible for considering the study according to the national legislation of their nation alone. However, the reviewer must highlight to the other participating UK nations where there are differences in legislation that will need to be considered.

The differences in legislation across the UK are detailed below:

<table>
<tr><th>When working in [Country] with...</th><th>England</th><th>Scotland</th><th>Wales</th><th>Northern Ireland</th></tr>
<tr><td>Adults unable to consent for themselves (non-CTIMP)</td><td>The Mental Capacity Act 2005 applies</td><td>The Adults with Incapacity (Scotland) Act 2000 applies</td><td>The Mental Capacity Act 2005 applies</td><td>No equivalent legislation</td></tr>
<tr><td>Human Tissue and Licensing</td><td>The Human Tissue Act 2004 applies</td><td>The Human Tissue (Scotland) Act 2006 applies to tissue from the deceased. The Human Tissue Authority’s remit and licensing requirements in</td><td>The Human Tissue Act 2004 applies</td><td>The Human Tissue Act 2004 applies</td></tr>
</table>
</td><td>IRAS application

Participant consent form

Participant information sheet

Research protocol or project proposal</td></tr>
</table>

		relation to research do not extend to Scotland except in relation to DNA		
Language	No equivalent legislation	No equivalent legislation	Welsh Language Act 1993 applies	No equivalent Legislation*

*A Mental Capacity Bill (NI) is under consideration and therefore there may be forthcoming changes.

There is potential that approval from other bodies should be in place before HRA Approval can be issued (e.g. National Offender Management Service where NHS staff are delivering a service in relation to offenders/prisoners). Such bodies may have their own expectations for research to take place (see also 6.4 below). The HRA will assess whether such approvals should be in place for studies applying for HRA Approval. Where they are, HRA Approval will not be issued until they are in place.

Study-wide considerations

Adults unable to consent for themselves (non-CTIMP)

Confirm the study has received favourable opinion from an appropriate Research Ethics Committee (REC) i.e. a REC that has been flagged to review "Research Involving Adults Lacking Capacity."

Research conducted in England / Wales and Scotland requires separate approvals under the Mental Capacity Act and the Adults with Incapacity (Scotland) Act 2000 respectively. Separate applications should be made to flagged RECs in each jurisdiction. In Scotland, the application should be made to the Scotland A REC and should include a patient information sheet and consent form for the guardian, welfare attorney or adult's nearest relative. If the research is taking place in England and /or Wales and / or Northern Ireland, there should be only one application. This should be made to a recognised REC in England or Wales. The REC will liaise with a committee in Northern Ireland in reviewing the documentation to be used in Northern Ireland. The usual practice is for an assent form to be used to seek agreement from relatives in Northern Ireland to recruit a person lacking capacity.

In assessing compliance with the Mental Capacity Act, the assessor will expect applications for non-CTIMPs seeking to recruit adults lacking capacity to be clear on the arrangements for seeking the advice of a consultee. This should be clear enough for the research team to easily understand the arrangements. In addition, where participants in a non-CTIMP are to be considered at high risk of losing capacity to consent whilst on study, the actions to be taken by research staff were this to occur should be explicit, particularly as to whether and how the participant may remain on the study as well as to what will happen with any data and/or material collected to that time. **Human Tissue and Licensing** When a study involves human tissue the most important considerations are: ▪ Is the study using existing or new human tissue samples or both? ▪ The consent required to use the human tissue samples ▪ The licensing required to use/ store the human tissue samples ▪ The handling of human tissue samples ▪ The arrangements for subsequent storage or disposal of samples Outline the use of human tissue in the study taking into account the considerations above and confirm if the use of human tissue meets the requirements set out by legislation (see notes). In assessing for compliance with the Human Tissue Act, the HRA will expect the application to clearly describe the arrangements for obtaining, processing, packaging, transporting and storing materials, including any arrangements for storage for future research. It should be clear how information governance requirements and expectations will be met (e.g. how and when will material be pseudonymised or anonymised?). Additionally, where material is being transported outside of the participating organisation, it should be clear whether and how the material will be returned, retained or destroyed and whether this will be under the material transfer provisions of the statement of activities (only for non-commercial studies) or other agreement/arrangements. Where material is to be rendered acellular (and thereby no longer be relevant material for the purposes of the Human Tissue Act), it should be clear when and where this will occur.	

Language

Where the study is to take place in Wales, this should be highlighted to the reviewers in Wales to consider this before satisfying the check (see notes).

Notes/Resources

Adults unable to consent for themselves (non-CTIMP)

This applies to any intrusive* research, wherever it takes place, except for clinical trials of investigational medicinal products (CTIMPs). Intrusive research is the type of research that would be unlawful if it was carried out "*on or in relation to a person who had capacity to consent to it, but without this consent".*

* Intrusive relates to the Mental Capacity Act only, in Scotland it applies to any research involving adults lacking capacity

In England & Wales

- Approval under Section 30 of the Mental Capacity Act must be sought from a recognised REC.
- A *personal or nominated consultee* **provides ADVICE** on the assumed will of the adult.
- An information sheet and **DECLARATION FORM** for the consultee is needed.

In Scotland

- Approval under the Adults with Incapacity (Scotland) Act must be sought from the Scottish A REC.
- The *guardian, welfare attorney or adult's nearest relative* **provides CONSENT** on behalf of the adult.
- An information sheet and **CONSENT FORM** for the guardian, welfare attorney or adult's nearest relative is needed.
- If an amendment is submitted that involves Adults with Incapacity, for the first time, the amendment must be submitted to Scotland A REC.

In Northern Ireland

- Section 30 approval from England/ Wales will suffice as the REC will liaise with the committee in Northern

Ireland to agree the assent form for relatives to allow recruitment.

NB: Studies reviewed by a Scottish REC must also be reviewed by an appropriate REC in England or Wales.

Human tissue and Licensing

(i) When a study involves human tissue, the following applies:

- England, Wales and Northern Ireland – The Human Tissue Act 2004.
  The Human Tissue Act 2004 sets out a legal framework for regulating the storage and use of human organs and tissue from the living, and the removal, storage and use of human organs, tissue and cells from the deceased, for specified health-related purposes including '**research in connection with disorders or the functioning of the human body**'.
  http://www.hta.gov.uk/licensingandinspections/listoflicensedestablishments.cfm

- Scotland – The Human Tissue (Scotland) Act 2006 applies to tissue from the deceased.
  For research purposes **this Act sets out provisions for the use of organs, tissues and samples (including skin, nails and hair) from the deceased**, i.e. body parts or fluids that are removed post mortem, and are subsequently used for research. **For research, it does not regulate the use of tissue from the living.**
  In relation to DNA the relevant section of The Human Tissue Act 2004 applies in Scotland (ie it is an offence to analyse DNA without the consent of the person from whom the tissue came or of those close to them if they have died.

- The consent required to use the human tissue samples
  In England, Wales and Northern Ireland
  Existing samples
    - Consent is required to store or use human tissue from the living for research unless:
      - It is obtained before 01 September 2006, or

- It is from the living and is NON-IDENTIFIABLE to the research and is for a specific project approved by a Research Ethics Committee.

- Consent is required to store or use human tissue from the deceased for research unless:
  - It was obtained before 01 September 2006.

For the deceased "appropriate consent" is sought. "Appropriate consent" means:

- The consent of the deceased person given before death,
- If there was no prior consent by the deceased person, the consent of a nominated representative,
- If no representative was appointed, a person in a qualifying relationship (i.e. family members and occasionally friends).
- For a deceased child the person who had parental responsibility immediately prior to the child's death or another person in a qualifying relationship

Persons in a qualifying relationship are ranked according to the closeness of relationship to the deceased.

- For tissue obtained before 01 September 2006 it is considered best practice to consent for the use of human tissue samples, but consideration must be given to:
  - The feasibility of identifying and re-contacting tissue donors
  - Any distress that may be caused through reminding tissue donors/ relatives of serious illness or injury
  - Any clinical significance that the research may have for the tissue donor

<u>New samples</u>

- Informed consent is always required to remove, store and use human tissue from the living for research.

○ For the deceased "appropriate consent" is sought to remove, store or use human tissue for research unless: ▪ The person died more than 100 years ago. *In Scotland* <u>Existing samples</u> ○ Consent is legally required for research if the tissue is: ▪ From a living person and samples are identifiable; or ▪ From a living person and samples are anonymised but there is no approval from a Research Ethics Committee ▪ From a deceased person and collected after 01 September 2006 (for both anonymous and identifiable samples). ○ The following material is exempted from the requirements of the Act and can legally be used for research without consent: ▪ Existing samples obtained before 01 September 2006, including any identifiable or anonymous material from the living or deceased. ▪ The licensing required to use/ store the human tissue samples *In England, Wales and Northern Ireland* <u>Living donors</u> ○ A licence is required to store human tissue from the living for research in connection with disorders or the functioning of the human body unless: ▪ It is for a specific project approved by a Research Ethics Committee (or pending approval) ▪ Storage is incidental to transportation ▪ It is stored with the intent to render the sample acellular <u>Deceased donors</u>	

- A licence is required to store human tissue from the deceased for research in connection with disorders or the functioning of the human body unless:
  - It is more than 100 years old
  - It is for a specific project approved by a Research Ethics Committee (or pending approval)
  - Storage is incidental to transportation
  - It is stored with the intent to render the sample acellular

[ACELLULAR: Acellular products are tissue-derived products that have been formed by cells but have been rendered acellular during processing. They include but are not limited to:

a) Demineralised bone matrix;
b) Sterile bone chips;
c) Irradiated cancellous bone
d) Acellular skin material

Other examples are listed on the Human Tissue Authority website (www.hta.gov.uk)

The Human Tissue Authority maintains Lists of licensed establishments according to the activities the establishments carry out. PDF listing of the licensed establishments can be downloaded by sector from the Authority's website at: http://www.hta.gov.uk/licensingandinspections/listoflicensedestablishments.cfm

In Scotland

- There is no licensing scheme in Scotland.

iii) The handling of human tissue samples licensing required to use/ store the human tissue samples

In England, Wales and Northern Ireland

- The Human Tissue Authority's Code of Practice for Import and export of human bodies, body parts and tissue says that the designated individual is responsible for ensuring a Service Level Agreement (SLA) or Material Transfer Agreement (MTA) is in place with the end user, confirming the requirements, processes and systems that should be in place for import to and export from England,

Wales and Northern Ireland. *In Scotland* - Although there is no licensing scheme in Scotland a NHS National Research Scotland Material Transfer Agreement should be in place for all tissue involving a designated Biorepository. **Language** The Welsh Language Act (1993) establishes the principle that the Welsh and English languages should be treated on a basis of equality, in the conduct of public business in Wales. Since 2011, the requirement to satisfy the Welsh Language Act governance check has been that confirmation that the study Participant Information Sheet and Participant Consent Form will be translated into Welsh/ provided bilingually, should this be requested by a participant at a research site. At the time of publication the NISCHR Academic Health Science Collaboration (AHSC) are undertaking a scoping exercise to establish a Wales wide translation service that would enable consistent translation of patient facing documents and would facilitate a streamlined approach to compliance with the Welsh Language Act (1993). An addendum to this guidance regarding the translation of participant information sheets and consent forms will be added once this scoping exercise is completed.	

6. Approvals and authorisations

6.1 NHS Research Ethics Committee favourable opinion received for applicable studies

Considerations	Source
Introduction	REC favourable opinion letter and

The Governance Arrangements for Research Ethics Committees (2011) – GAfREC, sets out the requirements and expectations for the ethical review of research to be conducted in the NHS. The following Research Ethics Committees (RECs) are established in accordance with GAfREC: ▪ All RECs appointed within the National Health Service and Northern Ireland Health and Social Care Service ("NHS RECs"). ▪ The Gene Therapy Advisory Committee (GTAC). ▪ The Social Care Research Ethics Committee for England. All these RECs are able to review research within the NHS but in some cases the remit is limited: ▪ Under paragraph 2.3.13 of GAfREC, review by a NHS REC is not normally expected for research involving healthcare or social care staff recruited as research participants by virtue of their professional role. There are certain scenarios where NHS REC review for such studies[3] would be expected because they raise a significant ethical issue or another provision of GAfREC applies. ▪ The GTAC reviews gene therapy research, research into stem cell therapy derived from stem cell lines, and trials of other advanced therapy medicinal products, and is incorporated into NHS RECs. The GTAC can transfer applications to other RECs recognised for the review of these study types. ▪ Social Care REC for England can review social care research involving NHS patients/staff or NHS research involving social sciences methodology, provided the research does not involve any change to standard clinical care. For social care research led from another UK nation, the review should be conducted by a NHS REC. 'Recognised' RECs are recognised by the United Kingdom Ethics Committee Authority (UKECA) for the review of clinical trials of investigational medicinal products (CTIMPs), in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004, for the class of research and geographical area indicated. Recognised RECs can also review non-	all correspondence

[3] Further information on when review by an NHS REC would be expected or required can be found in the Health Research Authority (HRA) National Research Ethics Service (NRES) guidance "Does my project require review by a Research Ethics Committee?"

CTIMP research. Authorised RECs are established under the Governance Arrangement for Research Ethics Committees (GAfREC) but not recognised by UKECA for the purposes of reviewing CTIMPs. An authorised REC may review all applications except those relating to CTIMPs. Certain types of study (medical devices, adults lacking capacity, prisoners, research funded by the US DHHS or one of its agencies) may be reviewed by a 'flagged' REC with specific expertise in the relevant area. The Ministry of Defence (MoD) REC is not established by the Department of Health. It reviews research sponsored by MoD or its agencies, or recruiting through the UK Armed Forces. Where participants are transferred into the NHS separate review by another REC would not be expected. For studies requiring review by a REC, the review of an application for ethical opinion can be carried out in parallel to the review for the NHS. For studies requiring review by a REC, the NHS organisation should not allow the study to start until the study has been granted a favourable opinion by the REC. For studies for which an NHS REC review is expected, HRA Approval will not be issued before a REC favourable opinion is in place, including confirmation that any applicable conditions have been met. If the HRA assessment is not complete when the REC issues their favourable opinion, the applicant will be notified of any outstanding questions or information expected from them to allow the assessment to be completed and HRA Approval issued. If the outcome of the REC review is a provisional or conditional opinion, the applicant will be notified of the status of	

the HRA assessment (e.g. complete or ongoing and, if ongoing, detail on what more is expected). If an unfavourable opinion is given by the REC, the applicant will be notified of the outcome of the HRA assessment at that point, to assist with any future resubmission of the study. **Study-wide considerations** For studies requiring or otherwise expected to receive review by a NHS REC, confirm the REC favourable opinion has been granted by the appropriate REC. It is not recommended that all documents submitted/ listed on REC letters are reviewed, only those relevant to the study wide considerations. ▪ Has the REC favourable opinion letter and all correspondence been received? *It is important that the REC favourable opinion letter and all correspondence is collated and distributed to all participating nations to ensure that :* *a) Any queries raised and addressed as part of the REC review are not re-examined unnecessarily* *b) The applicant is unable to revise a study document leaving out information previously requested by the REC.* When reviewing if the REC favourable opinion letter has been received, consideration should be given to the following: a) REC favourable opinion without additional conditions A REC favourable opinion letter without additional conditions should be accepted as received. i. Confirm that the documents received with the IRAS application match (including version numbers and dates) those granted approval as part of the REC favourable opinion. b) REC favourable opinion with conditions A REC favourable opinion letter may be received indicating conditions as part of the favourable opinion. i. Confirm that there is evidence that the conditions of the favourable opinion have been met.	

ii. If appropriate, correspondence between the Chief Investigator/ Sponsor and the REC related to addressing any conditions should have been received. iii. The related correspondence between the Sponsor/ Chief Investigator and the REC should be assessed to ensure that any changes to the document set have not impacted upon the outcome of the assessment c) REC provisional opinion with request for further information, clarification or revision During their ethical review the REC may issue a provisional opinion with a request for further information, clarification or revision relating to the application. i. If the REC has issued a provisional opinion with a request for further information clarification or revision this should be highlighted to the research site. ii. The related correspondence between the Sponsor/ Chief Investigator and the REC should be received to confirm that the requests of the provisional opinion have been addressed in the REC issuing their favourable opinion letter. iii. Where the REC has requested revision to the application, confirm the revised information has been received as part of the IRAS application. iv. The related correspondence between the Sponsor/ Chief Investigator and the REC should be assessed to ensure that any changes to the document set have not impacted upon the outcome of the assessment d) Amendments i. Confirm that any substantial amendments that should have been reviewed by the REC for continued favourable opinion have been granted continued favourable opinion. ii. Confirm the REC continued favourable opinion letter lists the documents that were reviewed and granted approval as part of the favourable opinion for the amendment. iii. Confirm that the documents received with the IRAS application match those granted approval as part of the REC continued favourable opinion.	

Notes/Resources Governance arrangements for research ethics committees https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213753/dh_133993.pdf Certain conditions detailed within REC favourable opinion letters are standard and should not be considered to be additional conditions. These include obtaining local management permissions and regulatory approvals where applicable.	

6.2 CTIMPs – Clinical Trial Authorisation (CTA) letter received

Considerations	Source
Introduction No clinical trial of investigational medicinal product (CTIMP) in the UK can be started or carried out, recruit participants or advertise to recruit participants until it has been authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) and has been given a favourable opinion by an NHS Research Ethics Committee (REC). For certain types of trials (see notes) notification to the MHRA is possible under the Clinical Trial Notification Scheme. For those trials eligible for the Notification Scheme the MHRA acknowledge the application with an accompanying note stating the trial may go ahead 14 days from the receipt of notification of no objections having been raised. The Sponsor is responsible for determining whether a research study is a CTIMP requiring a Clinical Trial Authorisation from the MHRA. The MHRA review of an application for Clinical Trial Authorisation can be carried out in parallel to the review for the NHS and REC. There is no expectation that the Sponsor supply a copy of the application for Clinical Trial Authorisation, submitted to the MHRA, to the NHS for review as well.	Clinical trial authorisation (or acknowledgement letter, where appropriate) from MHRA and relevant correspondence Amendments notification

The NHS organisation should not allow the study to start until the CTIMP has been granted Clinical Trial Authorisation (or equivalent under the Clinical Trial Notification Scheme), including sponsor confirmation that any conditions imposed have been met. Risk-adapted review For certain types of 'Type A' trials, authorisation is not required and a notification is sufficient. These are trials involving medicinal products licensed in any EU Member State if: ▪ they relate to the licensed range of indication, dosage and form ▪ or they involve off-label use (such as in paediatrics and oncology, etc) if this off-label use is established practice and supported by sufficient published evidence and / or guidelines. The notification consists of the standard EudraCT application form and accompanying documents. This will be acknowledged by the MHRA with an accompanying note to say that the trial may go ahead after 14 days from receipt of notification, if the MHRA has not raised any objections. This means that the acknowledgement letter will act as the authorisation. For studies requiring MHRA CTA, HRA Approval will not be issued before the MHRA CTA has been issued and the sponsor has confirmed in writing that any conditions on the CTA have been met, including evidencing this where requested. There is no expectation that the applicant send their MHRA CTA to the HRA, as these will be communicated directly, although the HRA may choose to contact the applicant to confirm that any applicable conditions have been met. **Study-wide considerations** Confirm the CTIMP has been granted Clinical Trial Authorisation by the MHRA. For trials that fall under the Clinical Trial Notification Scheme the acknowledgement letter from the MHRA acts as the authorisation as long as no	

objections have been raised by the MHRA. ▪ Has the MHRA Clinical Trial Authorisation letter for the CTIMP been received? When reviewing if the MHRA Clinical Trial Authorisation letter for the CTIMP has been received, consideration should be given to the following: a) Clinical Trial Authorisation without conditions A MHRA Clinical Trial Authorisation letter without conditions should be accepted as received. b) Clinical Trial Authorisation with conditions A MHRA Clinical Trial Authorisation letter may be received indicating conditions as part of the authorisation. i. Confirm that there is evidence that the conditions of the Clinical Trial Authorisation have been met. ii. If appropriate, correspondence between the Sponsor and the MHRA related to addressing any conditions should have been received. c) Clarifications made in the application submitted to the MHRA for Clinical Trial Authorisation During their review of an application for Clinical Trial Authorisation the MHRA may request clarifications in relation to the application. i. If correspondence is received relating to any clarifications made in application submitted to the MHRA for Clinical Trial Authorisation, the clarifications should be highlighted to the research site. ii. In some cases it may not be appropriate to view all correspondence between the Sponsor and the MHRA, as the correspondence may be commercially confidential or not relevant to the NHS. d) Amendments Confirm that any substantial amendments requiring review by the MHRA for continued Clinical Trial	

Authorisation have been granted continued authorisation and ensure that any impact of any changes has been accounted for. **Notes/Resources** For eligibility for the MHRA Notification Scheme http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf MHRA letters granting authorisation are sent unsigned.	

6.3 Devices – MHRA Notice of no objection received

Considerations	Source
Introduction The sponsor is responsible for determining whether a study involving a medical device is an investigation that requires a notice of no objection from the Medicines and Healthcare products Regulatory Agency (MHRA). A Notice of No Objection must be obtained from MHRA Devices for 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.	MHRA 'Notice of No Objection' letter (medical devices) and relevant correspondence

The MHRA review of an application for Medical Device applications can be carried out in parallel to the review for the NHS and REC. There is no requirement for the Sponsor to supply a copy of the Medical Device application, submitted to the MHRA, to the NHS for review as well. The NHS organisation should not allow the study to start until the Medical Device application has been granted a Notice of no objection. For studies requiring an MHRA notice of no objection, HRA Approval will not be issued before the MHRA notice of no objection has been issued and the sponsor has confirmed in writing that any conditions on the notice have been met, including evidencing this where requested. There is no expectation that the applicant send their MHRA notice of no objection to the HRA, as these will be communicated directly, although the HRA may choose to contact the applicant to confirm that any applicable conditions have been met. **Study-wide considerations** Where required confirm the Medical Device application has been granted a Notice of no objection by the MHRA. ▪ Has the MHRA Notice of no objection letter for the Medical Device application been received? When reviewing if the MHRA Notice of no objection has been received, consideration should be given to the following: a) Notice of no objection without conditions A MHRA Notice of no objection letter without conditions should be accepted as received. b) Notice of no objection with conditions A MHRA Notice of no objection letter may be received indicating conditions as part of the authorisation.	

i. Confirm that there is evidence that the conditions of the Notice of no objection have been met. ii. If appropriate, correspondence between the Sponsor and the MHRA related to addressing any conditions should have been received. c) Clarifications made in the Medical Device application submitted to the MHRA During their review of a Medical Device application the MHRA may request clarifications in relation to the application. iii. If correspondence is received relating to any clarifications made in Medical Device application submitted to the MHRA, the clarifications should be highlighted to the research site. iv. In some cases it may not be appropriate to view all correspondence between the Sponsor and the MHRA, as the correspondence may be commercially confidential, not relevant to the NHS. d) Amendments Confirm that any substantial amendments requiring review by the MHRA for continued Notice of no objection have been granted a continuation of the no objection and ensure that any impact of any changes has been accounted for.	

6.4 Other regulatory approvals and authorisations received

Considerations	Source
Introduction There are some occasions where other regulatory approvals and authorisations are required for research studies. Where this is the case the reviewer should also consider these alongside any other regulatory approvals and authorisations that are applicable to the research study. As per 5.3 above, HRA Approval will not be issued until any other applicable regulatory approvals are in place (e.g.	IRAS application Research protocol or project proposal

NOMS approval, CAG approval etc.).

Administration of Radioactive Substances
Under the Medicine (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 the 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.

The Health Research Authority application to the ARSAC consists of a project ('Preliminary Research Assessment (PRA)') form and a shorter site specific ('Research Certificate Application (RCA)') form. The PRA form should be submitted by the sponsor's representative to the ARSAC Support Unit as soon as the application for ethical review has been submitted. The RCA form(s) may then be submitted by the local certificate holder(s).

Accessing patient information without consent
The Health Research Authority's (HRA) Confidentiality Advisory Group (CAG), http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/, has been established to provide independent expert advice to the HRA on whether applications to access confidential patient information without consent for research should or should not be approved.

The role of CAG is to review applications and advise whether there is sufficient justification to access the requested confidential patient information. Applications to the CAG are required for access to:

- 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
- Central Register (formerly NHSCR) information (either with or without consent), or
- Hospital Episode Statistics / Secondary Uses Services (HES/SUS) for either identifiable or sensitive data (either with or without consent), or
- Human Fertilisation and Embryology Authority (HFEA) Register Data

The Health Research Authority Confidentiality Advisory Group should also be informed of substantial amendments to the study, for example to the study design or methodology, as the Section 251 support may be affected by the amendment. Substantial amendments should normally be submitted using the same information sent to the Research Ethics Committee or by letter. The amendments are then considered by the group who will confirm continued Section 251 support. All amendments, substantial or non-substantial must be listed in the annual review that the applicant should submit to the group.

In Scotland

- Approval is sought from the National Services Scotland, Privacy Advisory Committee for access to ISD data. http://www.nhsnss.org/pages/corporate/privacy_advisory_committee.php
- The Scottish Health Boards might also expect that Caldicott Guardian approval is sought and obtained.

In Northern Ireland

- Applicants should refer to the Privacy Advisory Committee (Northern Ireland) Code of Practice.
- Approval from the Medical Directors of the Northern Ireland Health and Social Care Trusts should be obtained.

Accessing Criminal Offenders

In England and Wales if the project is with Prisons or Probation Trusts an application to the National Offender Management Service (NOMS) should be sought via IRAS. Please refer to the NOMS website (http://www.justice.gov.uk/publications/research-and-analysis/noms) for more information.

The NOMS approval process extends to research in Young Offenders' Institutions (YOIs), but excludes research in Secure Training Centres, Secure Children's Homes or with Youth Offending Teams – applications to conduct research in these areas should be directed to the Youth Justice Board. http://www.justice.gov.uk/publications/research-and-analysis/yjb

Human Fertilisation and Embryology Authority

A licence from HFEA is required for:

- Research involving human embryos and gametes
- Disclosure of protected information from the HFEA Register

Human Tissue Authority (HTA, England and Wales)

The HTA does not approve individual projects or license activity itself but 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.

Organisations where clinicians or clinical units collect and supply samples or data to a research tissue bank or research database are not considered to be research sites. For example, a hospital may provide samples surplus to diagnostic use to a research tissue bank. If the sample or data is not collected specifically for the purposes of a particular research project then the organisation is a Tissue Collection Centre (TCC).

Study-wide considerations

ARSAC

As ARSAC certificates are issued at a site level there is no requirement for ARSAC certificates to be issued prior to completing the study-wide review. It may be appropriate to advise the applicant to submit the project-level Preliminary Research Assessment form http://www.arsac.org.uk/notes_for_guidance/index.htm. HRA Assessors will

confirm, where appropriate as suggested by the content of the application (i.e. use of ionising radiation medicinal product/s), whether a PRA has been submitted and, if not, whether it is intended that such submission will take place. If no application is intended, the HRA will obtain clarity on the rationale for this. **Accessing Patient Information without consent** Confirm the study has received the appropriate approvals to access patient information without the patient's consent. Each nation considers the request to access patient information without consent differently. The reviewer should also highlight that the approval to access patient information without consent may not be appropriate to another nation, and that the reviewers in those other nations should consider this before satisfying the check. **Accessing Criminal Offenders** Confirm the study has received the appropriate approvals to access criminal offenders. Each nation considers the access to criminal offenders for research studies differently. The reviewer should also highlight that the approval to access criminal offenders may not be appropriate to another nation, and that the reviewers in those other nations should consider this before satisfying the check. In England and Wales Confirm that a letter of approval from NOMS has been issued. In Scotland After obtaining clearance from the Scottish Prison Service Research Access and Ethics Committee (RAEC) applications for research proceed as per standard processes via IRAS. In Northern Ireland NOMS is not applicable to Northern Ireland. Advice on health and social care research involving prisoners in Northern Ireland, can be obtained from Paul.Carlin@setrust.hscni.net. **Studies funded by the US Department of Health and Human Services (DHHS)**	

Confirm that the study has been reviewed by an appropriate Research Ethics Committee (REC), i.e. a REC that has been flagged "IRB Registered." As well as being flagged to review research studies funded by the DHHS they must also be able to review the type of study being supported. For example, a clinical trial of an investigational medicinal product (CTIMP) with funding support from the DHHS must be reviewed by a committee that is both recognised to review the relevant type of CTIMP and registered with the OHRP. Details of the committees that are registered with the US Office for Human Research Protections (OHRP) can be obtained from the National Research Ethics Service (NRES) Central Allocation System (CAS). HFEA Confirm that an HFEA licence has been issued. HTA (England and Wales) Where the application refers to a licensed tissue bank, confirm that an HTA licence has been issued. Where the research involves collection of tissue from sites for a licensed research tissue bank, highlight that the sites are Tissue Collection Centres.	

DOCUMENT CHANGE RECORD

Version	Description
4.0, 31 March 2016	• Page 5, Level of capacity and capability assessment expected of participating organisations: Additional examples added to table. • Page 8, 1.1 IRAS application completed correctly: Updated reference to which studies are included within HRA Approval • Pages 11 and 12, 1.1 IRAS application completed correctly: Updated to reference to inclusion of student research within HRA Approval • Page 15, 2.1 Participant information / consent documents and consent process: Update to clarify use of stickers for localising patient documentation • Page 20, 4.1 Allocation of responsibilities and rights are agreed and documented: Additional reference to material transfer provisions in HRA Statement of Activities • Page 30, 4.3 Financial arrangements assessed: Assessment of HRA Schedule of Events included • Page 37, 5.1 Compliance with the Data Protection Act and data security issues assessed: Reference to US Safe Harbor Scheme removed and expectations around transferring Personal Data outside of EEA reworded • Page 43, 5.2 CTIMPs – Arrangements for compliance with the Clinical Trials Regulations assessed: Adults with incapacity in Scotland reference updated to align with UK wide RES SOP