Standard Operating Procedures for Research Ethics Committees

Version 8.1

16 June 2026

In partnership with the UK Health Departments Research Ethics Service:

Health Research Authority

Health and Social Care Northern Ireland

NHS Research Scotland

STANDARD OPERATING PROCEDURES

Contents

Introduction to RES SOPs – version 8.1

Purpose and scope

1. This document sets out standard operating procedures (SOPs) for Research Ethics Committees (RECs) within the UK Health Departments' Research Ethics Service (RES).[1]

2. Under the UK Health Departments' REC Policy Document each REC within the Research Ethics Service is required to adopt SOPs approved by or on behalf of its appointing authority. The REC is required to act in accordance with its SOPs and is ultimately accountable to its appointing authority for its governance in this respect.

3. The UK Health Departments have authorised the Health Research Authority to co- ordinate the development of operational systems for RECs, including the development of a UK-wide set of SOPs and the provision of operational advice and assistance.

4. These SOPs apply to and have been approved by the UKREDG and adopted by the appointing authorities for all RECs that are established in accordance with the REC Policy Document.

5. These SOPs meet the obligations of the Medicines for Human Use (Clinical Trial) (Amendment) Regulations 2025 ("The Clinical Trials Regulations"), and the International Council for Harmonisation Good Clinical Practice (ICH GCP) Guideline.

[1] The UK Health Departments are the Department of Health Research and Development Directorate (England), the Chief Scientist Office, Scottish Government Health Directorate (Scotland), the Welsh Government R&D Division (Wales) and the R&D Division, Public Health Agency (Northern Ireland).

6. The Medicines for Human Use (Clinical Trial) (Amendment) Regulations 2025 ("The Clinical Trials Regulations"), came into effect on 28 April 2026, replacing The Medicines for Human Use (Clinical Trials) Regulations 2004. UK RES also acts for the United Kingdom Ethics Committee Authority (UKECA) to provide a national mechanism for operational advice and assistance to RECs recognised for the purposes of the Clinical Trials Regulations.

7. The policy of the UK Health Departments is that the operating procedures required by the Clinical Trials Regulations should also apply in general to the review by RECs in the UK of all other health and social care[2] research reviewed under the REC Policy Document. There are some differences in operating procedures between CTIMPs and other research; these are indicated in the text where applicable.

8. These SOPs do not apply to RECs which are not part of the UK Health Departments' Research Ethics Service (for example RECs established by higher educational institutions or professional bodies). Other RECs and their appointing bodies are free to adopt relevant parts of these SOPs if they wish to do so, with acknowledgement.

9. The Ministry of Defence Research Ethics Committee (MoDREC) is established by the Ministry of Defence (MoD) and recognised by the United Kingdom Ethics Committee Authority (UKECA) for review of clinical trials under the Clinical Trials Regulations. MoDREC has adopted operating procedures which are set out separately by the MoD and are compatible with these SOPs.

Implementation

10. Version 8.1 of the RES SOPs is effective from 16 June 2026 and applies retrospectively to all research already underway with a favourable opinion from a REC. Where the SOPs state that a procedure "should" be followed - without qualification - all RECs adopting the SOPs will be expected to comply fully. Compliance will be monitored. The system of audit and accreditation of RECs is based on the REC Policy Document and the SOPs.

Terminology

[2] References in this document to "health and social care" should be taken to mean "health and community care" in Scotland.

11. A guide to the terminology used in the SOPs is set out prior to Section 1. The following should be noted in particular:

12. Responsibilities assigned in the SOPs to the “HRA Director/and or Deputy of the Approvals Service”, “Head of Approvals Operations” or “Head of Approvals Support and Improvement” may be delegated to another member of staff within the UK REC service.

13. All references in the SOPs to “the Chair” of the REC should be interpreted as referring also to the vice-Chair when acting in place of the Chair; or, if neither is available, to the alternate vice-Chair. If all three are unavailable, the REC’s appointing authority may appoint another member of the Committee to perform the duties of the Chair until one of the other Chairs becomes available. When the Chair (or a vice-Chair) is in the chair, the vice-Chair and alternate vice-Chair resume their status as members.

14. References to the Approvals staff/REC Manager should be interpreted as the equivalent role across the UK countries.

Back to contents

Terminology

Glossary

Adverse Reaction

In a CTIMP, any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. See also SSAR and SUSAR.

Anonymised

Anonymised in accordance with the Information Commissioner's Office anonymisation code

Appointing Authority

The body responsible for the establishment and support of a REC.

Appeal

Following the issue of an unfavourable opinion, the submission of the application without revision to another REC for a second ethics opinion

Appeal REC

The REC that reviews an application on appeal following the issue of an unfavourable opinion by the original REC.

Applicant

The individual submitting an application for review by an NHS Research Ethics Committee.

Approval conditions

Conditions to be met by the applicant prior to the start of the research. Approval conditions are issued by the REC in the final letter confirming a favourable ethics opinion. (Note: Approval conditions are distinct from further information requested from the applicant.)

ARSAC

Administration of Radioactive Substances Advisory Committee.

ASR

Annual safety report (see also DSUR).

ATMP
Advanced therapy medicinal product

Authorised REC
A REC established under the REC Policy Document but not recognised by UKECA as having the competence to review CTIMPs. An authorised REC may therefore review all applications except those relating to CTIMPs.

Booking
The booking of a new application for review by a REC, and reservation of an agenda slot. Bookings are made via IRAS.

CAG
The Confidentiality Advisory Group. The CAG provides independent expert advice to the Health Research Authority (for research applications) and the Secretary of State for Health and Social Care (for non-research applications) on whether applications to access patient information without consent should or should not be approved under Section 251 of the NHS Act (2006).

Care organisation
The organisation responsible for providing care to patients and/or users and carers participating in the study. Care organisations remain liable for the quality of care, and for their duty towards anyone who might be harmed by a study.

Chair
The member of a REC appointed to be Chair by the appointing authority. Where the Chair is unavailable for any reason, their duties may be performed by the vice-Chair or alternate vice-Chair.

Clinical Trials Regulations
The Medicines for Human Use (Clinical Trial) (Amendment) Regulations 2025.

Clock
The period allowed for the review of a new application or substantial modification. The clock starts on receipt of a valid application. For new applications, the clock may stop once to request further information from the applicant. The period of the clock depends on the type of study (see paragraphs 3.1-3.6). For substantial modifications, a 35-day clock applies in all

cases and the clock may stop to request further information from the applicant.

Complex Innovative Trials

A Complex Innovative Trial is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously. These trials are also sometimes referred to as platform, adaptive or umbrella trials. Complex Innovative Trial designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial.

CTA

Clinical Trial Authorisation - the authorisation from the MHRA to conduct a CTIMP. No CTIMP can commence in the UK without both a CTA and a favourable ethics opinion.

CTIMP

Clinical trial of an investigational medicinal product. (Any other type of research is known as a non-CTIMP).

CTIMP combined review

The combined and co-ordinated review process between the MHRA and REC.

DHHS

Department of Health and Human Services - the Federal Government department responsible for regulations on health research in the United States.

DMC

Data Monitoring Committee

DSUR

Development Safety Update Report - the common format for annual safety reports on investigational drugs in the ICH regions under ICH guideline E2F.

EAG

Expert Advisory Groups. These are panels of independent specialists convened to provide expert scientific and clinical advice on specific areas to support the MHRA in their approval process.

Electronic authorisation
Functionality provided by IRAS to allow IRAS account holders to notify that they agree with the declarations in applications generated by the system. The authorisations also act as a mechanism for verifying that the content of the applications remains unchanged from the point at which the authorisations were made.

Employing organisation
An organisation employing the Chief Investigator, other
investigators or research collaborators. Employers remain liable for the work of their employees.

HARP
HRA Assessment and Review Portal. The UK wide research ethics service database.

HRA
The Health Research Authority (in England). Established in the Care Act 2014 with functions relating to co-ordination and standardisation of practice relating to the regulation of research in health and social care, functions relating to ethics committees (appointing authority for English RECs), functions as a member of UKECA and functions relating to approvals for processing confidential information relating to patients.

HSC REC
HSC Health and Social Care is the term used in Northern Ireland for NHS. Therefore, NHS REC in Northern Ireland is known as HSC REC.

HTA
The Human Tissue Authority. The HTA regulates organisations that remove, store and use human tissue for research, medical treatment, post-mortem examination, education and training, and display in public

ICH
International Conference for Harmonisation, a collaboration between regulators and the pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

IMP

Investigational medicinal product.

Investigator's brochure

A document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product which are relevant to the study of the product in human participants.

IRAS

Integrated Research Application System - the on-line application system used to apply for most permissions and approvals for research in health and social care.

IRAS Project ID

The unique numerical identifier assigned to a research record in the Integrated Research Application System (IRAS).

Lead location

In the case of a multi-location study, the location for which the Chief Investigator is also the Principal Investigator.

Local collaborator

A person undertaking certain types of straightforward research procedures, not requiring the appointment of a Principal Investigator or a location agreement.

MHRA Medicines and Healthcare products Regulatory Agency

MHRA (Medicines) is the competent authority for the UK in relation to the Clinical Trials Regulations. MHRA (Devices) is the competent authority for the UK in relation to the Medical Devices Regulations 2002.

Minor Modification

Minor modifications are changes that do not fall into the category of 'substantial modification' or 'modification of an important detail'. This is not a term which is used in the Clinical Trial Regulations but is a term used by RECs to describe these types of modification.

These can be implemented anytime without informing the MHRA and REC, although other approvals (for example HRA & HCRW Approval) may be required.

Modification

A change made to the terms of the REC application, the protocol or any other supporting documentation after the study has started. A study is normally considered to start with the commencement of any protocol procedures. Modifications were previously referred to as 'amendments'.

MoDREC

The Research Ethics Committee established by the Ministry of Defence to review research involving the British Armed Forces or otherwise sponsored or funded by the MoD.

Non-CTIMP

Any research study that is not a CTIMP.

REC Policy Document

The UK Health Departments' policy document for research ethics committees (formerly known as 'Governance Arrangements for Research Ethics Committees – GAfREC').

RES

Research Ethics Service. The Research Ethics Service consists of Research Ethics Committees (RECs) across the UK reviewing health and social care research, volunteer members and chairs that sit on NHS/HSC RECs and staff.

OHRP

Office for Human Research Protections - a unit within the US DHHS responsible for implementing Federal Regulations relating to research funded by the DHHS or its agencies. This includes registration of Independent Ethics Committees / Institutional Review Boards and the Federal Wide Assurance (FWA) scheme for organisations hosting research.

Operational Manager

This could be the Scientific Officer in Scotland, the Head of the Office for Research Ethics Committees in Northern Ireland or an Approvals Operations Manager in England and Wales.

Participant

Patient, service user, carer, relative of the deceased, professional carer, other employee, or member of the public who consents to take part in a study. Under the Clinical Trials Regulations, the definition of a participant in a CTIMP is an individual, whether a patient or

not, who participates in a clinical trial either as a recipient of an investigational medicinal product (or of some other treatment or product) or without receiving any treatment or product, as a control).

PBPP
Public Benefit and Privacy Panel. The PBPP is a group that reviews applications to use health and social care data without consent in Scotland, ensuring that projects deliver public benefit while protecting individuals' privacy

Phase 1 trial
A clinical trial to study the pharmacology of an investigational
medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the participants of the trial.

Principal Investigator (PI)
The lead researcher for a research project at a particular location. Has responsibility for the conduct of the project at that location. In the case of a single-location study, the CI and the PI will normally be the same person.

Protocol
A document that describes the objectives, design, methodology, statistical considerations (or other methods of data analysis) and organisation of a research study.

REC
A Research Ethics Committee established in any part of the UK in accordance with the REC Policy Document and/or recognised by the UKECA under the Clinical Trials Regulations.

REC reference number
Reference number assigned by the REC accepting the application for review. This includes a REC local identifier, specific project number and year.

REC Manager/Approvals Staff
The staff member with first line responsibility for the professional oversight and support of one or more individual Research Ethics Committees. The term REC Manager applies in Scotland and Northern Ireland and the term Approvals Staff applies in England and Wales and will consist of either the Approvals Specialist or Approvals Administrator.

Receiving REC

The REC that first receives an application, whether or not it is then transferred to another REC for review.

Recognised REC

A REC legally recognised by UKECA to give an ethics opinion on a clinical trial of an investigational medicinal product (CTIMP) to be undertaken anywhere in the UK.

Referee

A person or body who gives expert advice to a REC on an application or any related matter.

Request for Further Information

If the REC is unable to issue a favourable ethical opinion after the initial review of an application or modification, it will request further information from the sponsor. For CTIMPs, the request may be joint with the MHRA.

Research location

The organisation or unit responsible for conducting any of the research procedures in a study at a particular locality.

SAE

Serious Adverse Event (see statutory definition below).

SCIE

Social Care Institute for Excellence.

Scientific Officers

Staff appointed by the Health Boards in Scotland to provide expert advice to RECs and R&D offices on the review of research proposals and manage REC centres.

Social Care REC

The national REC for review of adult social care research in England, appointed by SCIE. See Annex F.

SOPs

The Standard Operating Procedures issued by the HRA.

SSAR
Suspected Serious Adverse Reaction (see statutory definition listed below).

Substantial modification
A substantial modification requires the issue of a favourable opinion from the REC.

Under the Clinical Trials Regulations, a modification to a CTIMP that must be notified to the REC and/or MHRA. It requires a favourable opinion from the REC and/or approval from the MHRA before it can be implemented. The MHRA further classify substantial modifications into Route A or Route B modifications, but these classifications are not relevant to the REC review.

SUSAR
Suspected Unexpected Serious Adverse Reaction (see statutory definition listed below).

Transfer
The transfer of an application by the receiving REC to another REC for review.

UKECA
United Kingdom Ethics Committee Authority

UKREDG
UK Research Ethics Development Group. A group comprised of senior RES staff from England, Wales, Scotland and Northern Ireland.

Validation
An administrative check carried out by staff to verify that an application is complete and may be accepted for review.

Validation date
The date on which a valid application is received by a REC (see paragraph 1.44).

Working day
The clock start date is the working day on which a valid application or modification, or a complete response, is submitted to the REC. The working day is based on HRA office hours which are Monday – Friday (excluding Bank Holidays), 08:00-16:00.

Back to contents

Statutory definitions relating to CTIMPs

Note: The following is a selection of relevant definitions from The Medicines for Human Use (Clinical Trial) (Amendment) Regulations 2025 (“The Clinical Trials Regulations”), relating to clinical trials of investigational medicinal products (CTIMPs).

Chief Investigator

The Chief Investigator must be a health care professional and is the lead investigator who takes responsibility for the overall conduct of the trial:

(a) In relation to a clinical trial conducted at a single trial location it is the investigator for that location, or

(b) In relation to a clinical trial conducted at more than one trial location, this is a health care professional, whether or not that health care professional is an investigator at any particular location, who will take primary responsibility for the conduct of the trial.

Note: The formulation in (b) means that, in a multi-location study, it is lawful for the Chief Investigator to be an employee of a pharmaceutical sponsor company rather than one of the location investigators. The ethics review would need to ensure that they had appropriate professional qualifications and expertise to take responsibility for the conduct of the trial.

Clinical trial

Any investigation in human participants, other than a non-interventional trial, intended:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,

(b) to identify any adverse reactions to one or more such products,

(c) to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety or efficacy of those products.

Clinical trial protocol

A document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial.

Conducting a clinical trial

(a) Administering, or giving directions for the administration of, an investigational medicinal product to a participant for the purposes of that trial; or

(b) Giving a prescription for an investigational medicinal product for the purposes of that

trial; or

(c) Carrying out any other medical or nursing procedure in relation to that trial; or

(d) Carrying out any test or analysis:

(i) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of the investigational medicinal products administered in the course of the trial

(ii) to identify any adverse reactions to those products, or

(iii) to study absorption, distribution, metabolism or excretion of those products.

It does not include activity undertaken prior to the commencement of a trial which consists of making such preparations for the trial as are necessary or expedient.

Health care professional

A healthcare professional means any of the following:

Profession	Definition
Doctor	Registered medical practitioner
Dentist	Registered under the Dentists Act or entered in the list of visiting EEC practitioners under Schedule 4 to the Act
Nurse or Midwife	Registered nurse or registered midwife as defined in regulation 8(1) of the Human Medicines Regulations 2012
Pharmacist	Registered pharmaceutical chemist under the Pharmacy Acts 1952 and 1954, or Articles 6 and 9 of the Pharmacy (Northern Ireland) Order 1976
Ophthalmic optician	Registered under section 7 (a) of the Opticians Act 1989
Osteopath	As defined by section 41 of the Osteopaths Act 1993
Chiropractor	As defined by section 43 of the Chiropractors Act 1994

Physician Associates or Anaesthesia Associates	Registered under the Anaesthesia Associates or Physician Associates Order 2024.
Other healthcare professionals	Registered by the Health and Care Professions Council (as defined in regulation 8(1) of the 2012 Regulations) as a member of a relevant profession within the meaning of article 2 of, and paragraph 1 of Schedule 3 to, the Health Professions Order 2001. This provides for registration of arts therapists, biomedical scientists, chiropodists, clinical scientists, dieticians, medical laboratory technicians, occupational therapists, orthoptists, paramedics, physiotherapists, practising psychologists, prosthetists and orthotists, radiographers, speech and language therapists.

Investigational medicinal product

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

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

(b) used for an indication not included in the summary of product characteristics under the authorisation for that product

(c) used to gain further information about the form of that product as authorised under the authorisation.

Investigator

A health care professional who is responsible for the conduct of a trial at that location (of if there is more than one, all trial locations). If the trial is conducted by a team of health care professionals at that location or locations, the Investigator is the leader responsible for that team. The Investigator must be appropriately trained to undertake the role in a clinical trial.

Note: In the UK REC system, the term ‘Principal Investigator’ will be used for the lead investigator at a location. The terms ‘Investigator’ and ‘Principal Investigator’ are synonymous. There may be other local investigators at a location, who will be accountable to the Principal Investigator for the conduct of the trial.

Investigator’s brochure

A document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product which are relevant to the study of the product in human participants.

Modification of an important detail

This is a modification that does not significantly impact participant safety or rights, which the MHRA and REC only need to be made aware of for administrative or oversight purposes. These types of modification are not reviewed by the REC or MHRA and no outcome will be issued. They are for information only. These modifications may however need other approvals (for example HRA & HCRW approval).

Non-interventional trial

A study of one or more medicinal products which have a marketing authorisation, where all the following conditions are met:

(a) the products are prescribed in the usual manner in accordance with the terms of that authorisation,

(b) the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a clinical trial protocol,

(c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study,

(d) no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of the particular therapeutic strategy in question,

(e) epidemiological methods are to be used for the analysis of the data arising from the study.

Non-investigational medicinal product (NIMP)

A non-investigational medicinal product is a medicinal product that will be used in a clinical trial, as described in the protocol, but not as an investigational medicinal product.

Notifiable trial

A trial where there are no significant safety concerns with any of the investigational medicinal products (IMPs), as far as the sponsor is aware of having made reasonable enquiries. The full definition is set out in Regulation 11A of the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025. When the MHRA define a trial as notifiable, it is given automatic authorisation from the MHRA but there are no changes to the requirement for other regulatory reviews such as the REC review.

Phase 1 trial

A clinical trial to study the pharmacology of an investigational medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the participants of the trial.

Public Registry

A primary or partner registry of, or a data provider to, the WHO International Clinical Trials Registry Platform, provided that the registry, or the data provider, facilitates public access to information about the trial in the UK.

Serious adverse event

An untoward occurrence that:

(a) results in death

(b) is life-threatening

(c) requires hospitalisation or prolongation of existing hospitalisation

(d) results in persistent or significant disability or incapacity

(e) consists of a congenital anomaly or birth defect.

Specialist group or committee

This means a group or committee whose functions include the provision of advice on ethical or scientific issues in relation to:

- tissue engineered products,
- in the case of medicinal products for gene therapy or somatic cell therapy, the use of such therapies in the treatment of humans, or
- in the case of medicinal products containing genetically modified organisms, the administration of such products to humans;

Sponsor of a clinical trial

The person who takes on ultimate responsibility for the initiation, management and financing (or arranging the financing) of a clinical trial.

Note: The Clinical Trials Regulations allow for two or more persons to take responsibility for the functions of the sponsor. Where this applies, they require that one of the sponsors should take responsibility for each of the following functions:

(a) communications relating to substantial modifications and the conclusion of the trial

(b) communications relating to urgent safety measures

(c) pharmacovigilance reporting.

Substantial modification to a clinical trial authorisation

A modification to the clinical trial authorisation which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial

(b) the scientific value of the trial

(c) the conduct or management of the trial, or

(d) the quality or safety of any investigational medicinal product used in the trial.

Suspected serious adverse reaction (SSAR)

An “adverse reaction” is any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

An adverse reaction is “serious” if it:

(a) results in death

(b) is life-threatening

(c) requires hospitalisation or prolongation of existing hospitalisation

(d) results in persistent or significant disability or incapacity

(e) consists of a congenital anomaly or birth defect.

A “suspected serious adverse reaction” (SSAR), therefore, is any event which is suspected of meeting the above criteria.

Suspected unexpected serious adverse reaction (SUSAR)

A “suspected unexpected serious adverse reaction” (SUSAR) is a SSAR which is also “unexpected”, meaning that its nature and severity are not consistent with the information about the medicinal product in question set out:

(a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product

(b) in the case of any other investigational medicinal product, in the investigator’s brochure relating to the trial in question.

Back to contents

Section 1: New applications for ethics review

General requirements for submission of new applications

1.1. An application for ethics review of a research study should be made by the Chief Investigator (CI) for that study. Applications submitted via the combined review service are submitted jointly by the CI and the Sponsor. The CI should normally be professionally based in the United Kingdom. For international studies with a co-ordinating investigator outside the UK, a health care professional based in the UK should normally be nominated as the CI responsible for the conduct of the research in the UK. The REC may agree exceptionally to an application being submitted by a CI based outside the UK but should consider as part of the ethics review whether adequate arrangements are in place for supervision of the study in the UK. It is possible to accept a co-CI (joint lead applicants) as this can help less experienced researchers develop new skills. The details of the arrangement should be outlined in the application. Correspondence will only be sent to the lead applicant, therefore the individual named as the CI in the application form is responsible for passing on any information and sharing correspondence with their team.

1.2. Only one application for ethics review should be submitted in relation to any research protocol to be conducted within the UK (except where two applications are required for non-CTIMPs involving adults lacking capacity in both England/Wales/Northern Ireland and Scotland – see paragraph 13.38). In the case of international studies, an application must be made to an ethics committee in the UK, whether or not the study has a favourable ethics opinion from a committee outside the UK and whether or not it has started outside the UK.

1.3. In the case of research projects with separate protocols governing one or more sub- studies in addition to the main study, a full application should be submitted for each protocol. It is recommended that the parent study and any sub-studies are reviewed by the same REC wherever possible.

1.4. All new applications for ethics review to a REC in the UK should be submitted using IRAS.

Allocation of new applications

1.5. When ready to submit an application, the applicant should book a provisional slot at

a REC meeting. The applicant will be required to answer questions about the application to determine the type of REC which the application should be booked to. The first available meeting will be offered but applicants may choose a REC of choice (except for proportionate review applications). Tables A and B set out study types and the REC type to which they should be booked.

1.6. Applicants should book applications taking into account the guidance on allocation available within IRAS and on the HRA website; this guidance is based on the operational policy set out in Tables A and B. Further guidance on special allocations to flagged RECs is set out in paragraphs 1.11-1.15. Circumstances in which applications may be transferred to another REC, and the procedures to be followed, are described in paragraphs 1.54–1.64.

Clinical trials of investigational medicinal products (CTIMPs)

Table A. Clinical trials of investigational medical products (CTIMPs)

Type of CTIMP	Allocation
Phase 1 trial in healthy volunteers (including patients without the target disease or condition – see paragraph 1.18)	RECs which are recognised to review phase 1 studies involving healthy volunteers. Phase 1 studies involving healthy volunteers also have the option to book directly with the REC.
Phase 1/2a trial in both healthy volunteers and patients with the target disease or condition	Any recognised NHS REC
Phase 2a trials	Any recognised NHS REC
Trial of medicinal products for gene therapy	RECs which are recognised to review gene therapy trials.
Trial of Advanced Therapy Medicinal Product	RECs which are recognised to review gene therapy trials.

All other clinical trials of an investigational medicinal product in patients	Any recognised NHS REC.

Other research

Table B. Other research

Type of study	Allocation
Research involving prisoners or conducted within the prison services of the UK	Normally to a flagged REC in England and Wales if being conducted in England and Wales. Any REC in Scotland if being conducted in Scotland. Any REC in the UK if being conducted in Northern Ireland.
Research involving adults lacking capacity.	See detailed guidance in Section 13 Flagged REC.
Research involving children.	Any NHS/HSC REC
Research within the remit of the Social Care REC in England/Wales (see paragraph 1.22)	A REC in England/Wales which is flagged for Social Care research
Research involving patients/residents or information about patients/residents at Nursing Homes (Nursing Homes Regulations (Northern Ireland) 2005) or Independent hospitals/clinics/medical agencies (Independent Health Care Regulations	Any recognised REC in the UK.

(Northern Ireland) 2005) in Northern Ireland.	
Research involving patients/residents or information about patients/residents at Residential Care Homes (Residential Care Homes Regulations (Northern Ireland) 2005) in Northern Ireland.	Any authorised UK REC.
Research with funding from the US DHHS or one of its agencies (see paragraph 1.10)	Flagged REC for US DHHS-funded research.
Research involving medical devices.	Normally to a flagged REC.
Research tissue bank or research database. Renewal of Research Tissue Bank or Research Database applications.	Normally to a flagged REC. Normally to the REC which reviewed the original Research Tissue Bank or Research Database application.
All other applications.	Any NHS/HSC REC.
Research involving a social care setting in Northern Ireland in Nursing Homes (Nursing Homes Regulations (Northern Ireland) 2005) or Independent hospitals/clinics/medical agencies (Independent Health Care Regulations (Northern Ireland) 2005) in Northern Ireland.	Any recognised REC in the UK.
Research involving a social care setting in Northern Ireland in Residential Care Homes (Residential Care Homes Regulations (Northern Ireland) 2005) in Northern Ireland.	Any authorised UK REC.

Allocations to flagged RECs

Flagged RECs

1.7. "Flagged RECs" are RECs designated for review of particular types of application due to having relevant professional, academic and ethics expertise among the Committee's membership, including expertise acquired through training or previous experience in the relevant field of research ethics.

1.8. Flagging of RECs is in most instances an administrative arrangement. Recommendations on flagging of particular RECs are made by the Head of Approvals Support and Improvement, in consultation and agreement with the REC concerned, and approved by the UK Research Ethics Development Group (UKREDG). The Head of Approvals Support and Improvement is responsible for oversight of flagging arrangements, taking account of the number and geographical distribution of applications in the relevant field as well as changes in the membership of RECs. Potential changes to administrative flags should be considered and implemented when members providing the relevant expertise leave the Committee and when new members join the Committee. Lists of flagged RECs are available from the REC Directory page of the HRA website.

1.9. Administrative flags are currently in place for the following types of research:

a) Research involving children

b) Research involving prisoners[3] in England and Wales or otherwise conducted within His Majesty's Prison and Probation Service (HMPPS)

c) Research on medical devices

d) Research databases

e) Research tissue banks

f) Qualitative research

[3] A prisoner for this purpose means any person detained in the custody of HM Prison Service (i.e. within His Majesty's Prison and Probation Service for England and Wales). Prisoners do not include patients detained under the Mental Health Act at special hospitals or other psychiatric secure units, or juvenile offenders detained in local authority secure accommodation or secure training centres. This flag does not apply to review of research in the Scottish Prison Service or the Northern Ireland Prison Service.

1.10. In some instances, flagging of RECs is based on legal or regulatory authority for the review of a particular type of application, either as specified in statute or through recognition by a statutory authority. These legal and regulatory requirements are summarised in the table below.

Type of research	Geographical scope	Applicable REC(s)
Clinical trial of an investigational medicinal product	UK-wide	REC with appropriate type of recognition from UKECA (see paragraph 1.16)
CTIMP for gene therapy	UK-wide	REC with appropriate recognition
CTIMP involving adults lacking capacity	Scotland	A designated REC in Scotland (see paragraph 13.6)
Non-CTIMP involving adults lacking capacity	Scotland	Scotland A REC (see paragraph 13.32).
Non-CTIMP involving adults lacking capacity	England/ Wales or Northern Ireland	A REC in England/Wales or Northern Ireland.
Research involving patients/residents or information about patients/residents at Nursing Homes (Nursing Homes Regulations (Northern Ireland) 2005) or Independent hospitals/clinics/medical agencies (Independent Health Care Regulations (Northern Ireland) 2005) in Northern Ireland.	Northern Ireland	Any recognised REC in the UK.

Research involving patients/residents or information about patients/residents at Residential Care Homes (Residential Care Homes Regulations (Northern Ireland) 2005) in Northern Ireland.	Northern Ireland	Any authorised REC in the UK.
Social care research with no involvement of NHS patients or collection or use of their tissue/data	England or Wales	A REC in England/Wales which is flagged for Social Care research
Research funded by the US DHHS or one of its agencies	UK-wide	A REC with a current registration with the US DHHS's Office for Human Research Protections
Research involving a social care setting in Northern Ireland in Nursing Homes (Nursing Homes Regulations (Northern Ireland) 2005) or Independent hospitals/clinics/medical agencies (Independent Health Care Regulations (Northern Ireland) 2005) in Northern Ireland.		Any recognised REC in the UK.

Research involving a social care setting in Northern Ireland in Residential Care Homes (Residential Care Homes Regulations (Northern Ireland) 2005) in Northern Ireland.	Northern Ireland	Any authorised REC in the UK.

General policy on allocation to flagged RECs

1.11. Where a legal or regulatory requirement applies (as described in paragraph 1.10), it is mandatory for the application to be submitted to the particular REC or type of REC specified.

1.12. In addition, trials of stem cell therapy involving cells derived from stem cell lines must be submitted to a REC which is recognised to review gene therapy trials.

1.13. In all other cases, review by a flagged REC is strongly recommended to applicants.

1.14. Where a non-flagged REC is allocated an application that would normally be reviewed by a flagged REC, it should be considered whether the REC requires additional expertise to undertake the review, either through co-opting additional members or seeking advice in writing from a flagged REC or other referee.

1.15. Advice should be sought from an operational manager where there is doubt about the appropriateness of a particular REC allocation.

Allocation of CTIMPs to recognised ethics committees

1.16. A CTIMP must be reviewed by an ethics committee that (a) is recognised by UKECA under the Clinical Trials Regulations **and** (b) is recognised to review the appropriate type of CTIMP.

1.17. RECs which are no longer recognised to review new applications for CTIMPs continue to be recognised by UKECA to act as the REC for trials of which they previously gave a favourable opinion, including review of substantial modifications, safety reports and any other associated work. Where the REC is concerned that it does not have the necessary expertise, it may seek the advice of an appropriately flagged REC but should give the final decision itself. Applications must not be transferred to other RECs, nor should a different REC be asked to carry out the

formal review of a modification unless this has been authorised by the Deputy Director of the Approvals Service).

1.18. Phase 1 CTIMPs involving patients suffering from the disease or condition to which the trial relates can be reviewed by any recognised ethics committee. Phase 1 flagged RECs are only mandatory for the review of clinical trials where there is no intended therapeutic benefit for the participant, i.e. healthy volunteers.

Non-interventional trials of medicinal products

1.19. Trials of medicinal products which are "non-interventional" (see definition in the Glossary) are not classified as CTIMPs and do not require review by a recognised REC. They should be allocated in accordance with the normal procedures for non-CTIMPs.

Determining whether a study is a CTIMP

1.20. The Medicines and Healthcare products Regulatory Agency (MHRA) has published guidance on the interpretation of the statutory definition of a CTIMP and a non-interventional trial Where there is doubt about the classification of a trial, it is the responsibility of the Chief Investigator or sponsor to seek authoritative advice from the MHRA Clinical Trials Helpline, using the contact details on the MHRA website. (However, the REC may check directly with the MHRA by emailing ctdhelpline@mhra.gov.uk and providing a copy of the protocol). The REC should proceed with the ethics review but advise the applicant of the possible consequences if the application has been wrongly classified. If an application submitted as a non-CTIMP is in fact a CTIMP, the application should be withdrawn and re-submitted to a recognised REC Where a study is submitted as a non-CTIMP and given a favourable opinion, and it emerges later that it is in fact a CTIMP, corrective procedures are set out in Annex C.

Dual staff and patient studies

1.21. Studies which include both NHS and social care provider staff who are recruited through their professional capacity and NHS patients/service users, should be reviewed by a REC and an opinion given on the study as a whole. There is no requirement to ensure that the staff element of the study has been reviewed by a non-NHS REC prior to giving a decision.

Social Care Research

1.22. Applications originating in England or Wales which relate to social care should be

submitted to a REC flagged to review social care research. These RECs may also review social care research taking place in England and/or Wales and another UK country. Other RECs in England or Wales may not accept applications relating to social care research unless the study also involves NHS patients or collection or use of their tissue/data.

1.23. Research involving NHS patients and/or NHS staff, subject to paragraph 1.80, may be accepted for review by the Social Care REC where it uses social science methodology and does not involve any clinical interventions or changes in clinical practice. Where such applications are accepted for review, they do not then require separate review by another REC.

1.24. Where the project involves adults lacking capacity in Scotland as well as England/Wales or Northern Ireland, separate review is required by the designated REC in Scotland.

1.25. The ethics review of social care research is described in more detail in Annex F.

Ministry of Defence Research Ethics Committee (MoDREC)

1.26. The Ministry of Defence appoints a Research Ethics Committee to undertake ethics review of research involving the UK Armed Forces or otherwise sponsored or funded by the MoD:

> MoDREC is not part of the UK Health Departments' Research Ethics Service but operates to standards set out by the MoD which are compatible with those in the REC Policy Document and these SOPs. MoDREC is recognised by UKECA to review CTIMPs involving participants who are UK Armed Forces personnel recruited in a military setting, as well as Phase 1 trials in healthy volunteers conducted by the MoD or its agencies or contractors. MoDREC is also recognised as an Appropriate Body under the Mental Capacity Act 2005 for review of research involving UK Armed Forces personnel who are unable to consent for themselves.

1.27. Research within the remit of MoDREC should be submitted to MoDREC for ethics review rather than to a REC within the UK Health Departments' Research Ethics Service. Where an application within the remit of MoDREC is submitted in error to another REC, it should be transferred to MoDREC. Contact details for the MoDREC Secretariat are on the HRA website.

1.28. Where research with a favourable opinion from MoDREC continues within the NHS or adult social care sectors anywhere in the UK following transfer of participants into

their care, it does not then require separate ethics review by another REC unless review is required under the Adults with Incapacity (Scotland) Act 2000 or Mental Capacity Act (Northern Ireland) 2016.

Procedures for booking and submitting applications

1.29. When the application is ready to submit, the applicant should book an agenda slot at the next meeting of an appropriate REC.

1.30. Applicants should be offered the first available meeting slot at an appropriate REC in the UK (either a full meeting or a sub-committee for proportionate review, as appropriate). Studies which are suitable for proportionate review must be booked to the next available meeting in the UK.

1.31. For full meetings, the applicant may decline the first available slot in the UK if they have a preference for a particular REC (for example, it has reviewed an earlier phase of the trial).

1.32. Once the booking has been accepted, the application form and supporting documentation must be submitted the same day as the booking is made. Paper copies should not be accepted under any circumstances. An email confirmation of the booking will be sent to the applicant and to the REC to which the application has been allocated.

1.33. If the applicant is not ready to submit the application including all required authorisations and supporting documentation on the same day, the booking should not be completed.

1.34. Phase 1 studies booked directly with an appropriate NHS REC may be submitted at a later date (up to 7 calendar days before the REC meeting) by agreement with the Approvals Specialist/REC Manager.

1.35. Applications received up to 16:00 hours are considered to be received that working day. Applications received after 16:00 are considered to have been received the following working day.

Validation of applications

The validation date

1.36. The relevant period, within which an ethics opinion must be given (see paragraphs 3 – 3.4), begins when a valid application is received.

1.37. Subject to paragraph 1.39, the relevant date (“the validation date”) is the working day

on which the complete application is received, including all relevant authorisations and all supporting documents.

1.38. If the applicant has declined the next available agenda slot in order to secure a slot at their preferred REC, the validation date is the closing date for applications to the meeting to which the application is assigned.

Decision on validation

1.39. For non-CTIMPs, it is the responsibility of the receiving REC to decide whether or not the application is valid and to notify the sponsor within 7 calendar days of receiving the application. The appropriate validation checklist should always be completed in HARP. Where additional information or clarification is required in order to complete validation, these should be requested from the sponsor as soon as possible so that the validation outcome can be resolved within 7 calendar days. If these issues cannot be resolved within 7 calendar days, the application will be invalid (see paragraph 1.48), and the sponsor will need to resubmit the application.

1.40. For CTIMPs, the application is validated by the MHRA. The MHRA will confirm the validation status to the applicant. REC staff do not need to undertake a formal validation check but should check the application against the standard validation criteria (see 1.42) and request any missing information or clarifications from the applicant if required. This should be requested promptly so that it can be resolved and the application validated within 7 calendar days of receiving the application. If these issues cannot be resolved within 7 calendar days of receiving he application, the application will be invalid (see paragraph 1.48), and the sponsor will need to resubmit the application.

1.41. Where an application is transferred to another REC, responsibility for validation passes to the staff managing the REC to which the application is transferred (see paragraph 1.66).

Validation criteria

1.42. An application should be accepted as valid if it meets all the following criteria:

(a) The application form has been correctly completed in IRAS and submitted together with all supporting documents. (The checklist in IRAS indicates which documents are mandatory.)

(b) All relevant sections and questions in the application form have been completed, the text is in English and the print is clearly legible.

(c) The project filter has been completed correctly in IRAS.

(d) The application form has been electronically authorised in IRAS by the Chief Investigator and the authorised representative of the lead sponsor[4] (all applications); by the lead Medical Physics Expert and lead Clinical Radiation Expert[5] (research involving the use of ionising radiation); and by the academic supervisor (applications submitted by students). For Research Tissue Bank applications, the application form should be electronically authorised by the Tissue Bank Manager and the Designated Individual. For Research Database applications, the application form should be electronically authorised by the Data Controller and the Data Custodian.

(e) Short curriculum vitae (a maximum of two pages is recommended) have been submitted for the Chief Investigator (or the Tissue Bank Manager/Data Controller for Research Tissue Bank and Research Database applications), and in the case of student applications, for both the student and academic supervisor.

(f) A research protocol has been submitted. The protocol should be complete; it is not acceptable to submit modifications alongside the protocol except as permitted by paragraph 6.8.

(g) Supporting documents must be marked with version numbers and dates in the case of the research protocol, information sheets, consent forms, letters to participants or others with an interest in the research, and any other documentation to be used in the research that is not already scientifically validated and referenced (CVs and documents related to insurance, indemnity or funding should be dated but do not require version numbers.)

(h) The sponsor has been named on the application form. Where there is more than one sponsor, one of the co-sponsors must be named as the

[4] The lead sponsor may authorise any person to act as their representative for the purposes of making or supporting applications to the REC and other regulatory and governance bodies. The authorised representative will normally be a senior employee within the sponsor organisation, a trial manager at a Contract Research Organisation or a contract research consultant. Generic e-mail addresses for authorisations are permitted. Exceptionally it could be the CI or another member of the investigational team. If any doubt arises whether the person authorising the declaration has been duly authorised, staff may request evidence, e.g. a letter from the sponsor, or check with the sponsor directly. A list of authorised representatives is available on SharePoint.

[5] The signatories should provide their registration number.

lead sponsor for the purpose of correspondence on the REC application. If the named sponsor representative is a member of the REC to which the application has been allocated, the application must be transferred to a different REC.

(i) A copy of any available comments or scientific critique reports from referees or review committees should be provided with the application (if available) together with any correspondence which explains how issues raised by scientific critique have been resolved. If the applicant states that a copy of the report is not available, the application would still be valid as long as the free text box has been completed to specify how the study had been reviewed. In the case of research undertaken mainly for educational purposes, review by the academic supervisor is considered appropriate.

(j) In the case of a CTIMP, either the sponsor or the sponsor's legal representative is established within the European Economic Area.

(k) In the case of a CTIMP, where the sponsor has appointed a legal representative, evidence has been provided (in the form of a letter from the legal representative or contract with the sponsor) confirming that the legal representative has agreed to undertake this role. The legal representative may be a person or an organisation. No legal qualifications are required.

(l) Where an unfavourable opinion has been given to a previous application related to the same research project, the following criteria also apply:

(m) A copy of the unfavourable opinion letter has been provided.

(n) The application form or a covering letter explains how the new application addresses the reasons given for the unfavourable opinion.

(o) Any changes to study documents have been highlighted and documents given revised version numbers and dates where applicable.

1.43. If an application is received which is likely to attract interest from the media (e.g. if the application uses a controversial study design or methodology), an Operational Manager should be informed. Applicants are also encouraged to contact the REC in advance if they are aware that their study is likely to attract press attention.

Validation letters

1.44. When an application is valid, the Chief Investigator and sponsor should be notified.

1.45. A copy of the validation letter should be sent via email to the sponsor of the research application. Where more than one sponsor has been named on the application, only one of the sponsors needs to be notified. The application form should include the sponsor's or co-sponsors' main contact point for communications with the REC.

1.46. The validation letter includes an invitation to the Chief Investigator to attend the REC meeting (see paragraph 2.22). Details of the arrangements for the meeting should be inserted, including any specific information about meeting procedures.

Invalid applications

1.47. In the case of an invalid application, the Chief Investigator should be notified of the reasons. The application is void and should be removed from the assigned meeting in HARP (this does not apply for applications submitted via the CTIMP combined review service, the same meeting slot should be retained where possible). Time permitting, the meeting slot will then become available to be booked into. The Chief Investigator may re-book and re-submit the application, in which case it should be treated as a new application.

1.48. An application will be confirmed as valid or invalid within 7 calendar days of the application being received. Where information or documentation is missing which would make the application invalid, staff should follow this up as quickly as possible with the applicant. Where this occurs, the validation date is the date on which the last part of the information required for a valid application is received by the REC. The application should be marked as 'validation under consideration' on HARP (this applies to **all** applications which are invalid, and assistance is provided to try to make the application valid, regardless of what has been requested or the time it will take to make the application valid). If the application cannot be made valid within 7 working days, or prior to the cut-off date for the REC meeting (whichever is soonest), the application should be changed from 'validation under consideration' to 'invalid' on HARP and withdrawn from the meeting.

1.49. The reasons for the application being 'validation under consideration' should be recorded and saved on the validation checklist in HARP.

1.50. Applications should not be made available to REC members unless valid. For applications submitted via the CTIMP combined review service, applications may be provided to REC members if necessary whilst the outcome of the MHRA validation is awaited.

1.51. If the application is invalid, the normal procedures under paragraphs 1.48-1.49 apply.

1.52. Where the application has been allocated to a full meeting but following screening it is considered that it meets the criteria and no significant ethics issues have been presented warranting review by full committee, it may be re-assigned to a sub-committee for proportionate review. The Approvals Staff/REC Manager of the first REC is responsible for transferring the application. The appropriate member of staff should identify the next PR sub-committee meeting in the UK and transfer the application via HARP

Applications validated in error

1.53. Where an application has been validated in error, every effort should be made to address the matter with the applicant prior to the meeting. At the discretion of the Chair, further information may be distributed to members or tabled at the meeting. Wherever possible, the REC should proceed with the ethics review. Minor issues relating to the validity of the application may be addressed at the meeting or in the request made by the REC for further information or clarification following the meeting. Where part of the application form is missing, it is permissible to proceed with the review, however, submission of the form as part of a provisional opinion must be reviewed by sub- committee. If, however, the issues are fundamental, the application may need to be withdrawn or rejected.

Transfer of applications to another REC

Mandatory transfer

1.54. For both full and Proportionate Review applications, the REC that receives an application ("the receiving REC") should arrange for 'mandatory transfer' to another REC ("the second REC") as soon as possible in the following circumstances:

(a) The receiving REC does not have legal or regulatory authority to review the application (see paragraph 1.11).

(b) One of the members of the receiving REC is named in the application as the Chief Investigator, or another key investigator/collaborator in the research, or the named sponsor contact. (Mandatory transfer does not apply where the member or deputy member is the academic supervisor for a student applicant, but the interest should be declared under the procedures in paragraphs 2.47).

1.55. Before transferring the application, the Chief Investigator (CI) should be contacted to

explain the reasons for the transfer. The preferences of the CI should be considered in determining a suitable agenda slot at another REC. If the CI accepts the first meeting slot available, the validation date will remain the date that the valid application was received by the receiving REC. If the CI does not accept the first available meeting slot, the validation date will be the closing date for the meeting to which the application is assigned

1.56. For full applications, staff should complete as much of the validation process as possible before an application is transferred to a different REC. Staff from the transferring REC should relay any information relating to the validation status of an application to the receiving REC. When an application is received for Proportionate Review but is deemed unsuitable and needs to be transferred to a full REC meeting, the staff from the receiving REC should liaise with the applicant to arrange the transfer and should inform the second REC why the application is not suitable for Proportionate Review. The second REC is then responsible for validating the application. The receiving REC should transfer the application to the agreed full REC meeting and remove the application from the meeting as soon as possible to ensure Proportionate Review meeting slots are used as effectively as possible.

Optional transfer

1.57. In addition, the receiving REC may arrange for 'optional transfer' of an application for one of the following reasons:

(a) The next meeting of the REC is to be postponed or cancelled for operational reasons, e.g. a risk that it will not be attended by sufficient members.

(b) The application would be more appropriately reviewed by another REC.

(c) One of the members of the receiving REC is deemed to have a significant potential conflict of interest in relation to the application.

1.58. Optional transfers for operational reasons under paragraph 1.57(b) should normally take place only after consultation with the Chief Investigator and with their agreement. The Chief Investigator should be offered the opportunity to have the application transferred to another REC that is able to review the application earlier than if it were retained by the receiving REC. If the application is transferred, the validation date remains the date on which it was first received by the receiving REC. However, the Chief Investigator may opt not to transfer the application and to delay review of the application until the next available meeting of the receiving REC. In this

case the validation date will be the closing date for submissions to that meeting.

1.59. Although transfers under paragraph 1.57(b) should normally be with the Chief Investigator's agreement, it is possible to proceed with the transfer with appropriate approval from an Operational Manager if the Chief Investigator cannot be contacted.

1.60. An optional transfer under paragraph 1.57(b) or 1.57(c) should take place only after consultation with agreement from an Operational Manager. Advice should be sought on the re-allocation of applications requiring special expertise not available to the receiving REC.

1.61. In the case of optional transfers under paragraph 1.57(c) the validation date remains the date on which it was first received by the REC that transfers the application.

Re-allocation of transferred applications

1.62. Where a transfer is to take place, the receiving REC should notify the applicant by phone or email, explaining why the REC is unable to review the application. The applicant should be provided with the available meeting options before confirming the transfer.

1.63. Advice from an Operational Manager should be sought on the re-allocation of applications requiring special expertise not available to the receiving REC.

1.64. Once the new allocation has been confirmed on HARP, the documents will be transferred to the second REC. The member of staff from the receiving REC should contact the member of staff from the second REC to inform them that an application has been transferred.

Responsibility for validating transferred applications

1.65. Responsibility for validating a transferred application passes to the to the second REC, however, it is good practice for the receiving REC to inform the applicant of any validation issues when arranging the transfer.

1.66. The second REC should notify the applicant whether or not it is valid as soon as possible, and normally within two working days of the arrival of the transferred documentation. Where the receiving REC had already issued a validation letter before deciding on the need for transfer, a second validation letter should be sent. (If the application has been transferred to a REC in another region, the letter should carry a new REC reference number.) Where the application is re-allocated to the first available meeting of another REC, the validation date remains the original date of receipt by the receiving REC. However, where the Chief Investigator has declined

this option in favour of his/her preferred REC, the validation date is the closing date for the meeting of the preferred REC.

1.67. It is recommended that, wherever possible, the receiving REC should make an initial assessment of the validity of the application before a transfer takes place. Where the application is clearly invalid, the applicant should be notified and advised to submit a new application. This will avoid the need to transfer the documentation at this stage. Where the application appears to be valid, the receiving REC may pass on this advice by phone or email to the second REC. This will enable the receiving REC to issue the validation letter as soon as the documentation is received.

Revision of applications following submission

1.68. In general, revisions to an application that has been validated and booked for review should not be accepted. There are some exceptions to this such as when changes have been requested by the Proportionate Review Sub- Committee prior to confirming the ethics opinion, and where pre-meeting advice has been provided by a Scientific Officer (for applications in Scotland).

1.69. If the applicant considers it necessary to make significant revisions to the application form or the supporting documentation prior to review by the REC, the applicant should withdraw the application (see paragraph 1.78). Any minor revisions may either be discussed at the meeting or dealt with later in accordance with paragraph 1.77.

1.70. If the applicant considers it necessary to revise the terms of the application or supporting documentation following review by the REC but before a final ethics opinion has been given, these may be included in the applicant's letter in response to the REC's request for further information or clarification (see Section 3). For applications involving the NHS in England and Wales, this could include changes which have been requested by the Approvals Specialist in order to meet HRA assessment standards. Changes to supporting documentation should be clearly highlighted, and the relevant documents given a new version number and date. At the discretion of the Chair, the revisions may then be reviewed in accordance with the procedures agreed for considering further information from the applicant. Where, exceptionally, a substantial modification is submitted during the review process (see paragraph 6.8), it should be reviewed by the Chair/vice-Chair and at least one other member.

1.71. If the Chair considers the proposed revisions to be both ethically significant and unrelated to the matters raised by the REC in the ethics review, the applicant may be

advised to withdraw the application and re-submit it. Alternatively, the application may be rejected. It is not normally appropriate at this stage for the applicant to introduce significant new issues, which the REC will not have had the opportunity to review collectively.

1.72. For revisions made after a favourable opinion has been given, refer to the procedures for review of modifications in Section 6.

Submission of revised application forms

1.73. Submission of a revised application form is required as part of a new application following withdrawal of a previous application or issue of an unfavourable opinion.

1.74. It is also appropriate for the receiving REC to request a revised application form in the following circumstances:

(a) where the initial application is invalid because the application form is incomplete or otherwise fails to meet the requirements of a valid application;

(b) where a substantial modification requires submission of a new or revised section of the form for review;

(c) where there is a change to the Chief Investigator or sponsor (either during initial review or at any time during the study) and it is necessary for the declaration(s) in IRAS to be re-authorised and submitted to the REC with details of the new CI/sponsor.

1.75. Revised application forms should be submitted electronically via IRAS.

1.76. It is not normally appropriate to request a revised application form for any other reason. Where the REC raises questions about the content of the application form as part of a request for further information, applicants should provide any additional information, clarification or correction by letter.

1.77. Applicants may update or amend their integrated dataset in IRAS at any time in the light of changes requested by other regulatory and governance bodies or modifications made during the study and approved by the sponsor. This may result in changes to fields that populate the REC application form in IRAS. Where these changes meet the criteria for a substantial modification requiring ethics review, they should be notified to the REC by submitting a substantial modification. There is no need for the initial application form to be re-submitted.

Withdrawal of applications

1.78. If an applicant withdraws an application at any time, it should be recorded as 'withdrawn by applicant' in HARP. A clear reason, as provided by the applicant, should be entered on HARP. If the applicant wishes to re-submit the application, it should be re-booked via IRAS. A new REC reference number should be issued. A new clock commences when the valid application is re-submitted.

1.79. For applications submitted via the CTIMP combined review service, applications can only be withdrawn up to the point at which an initial outcome has been issued. If an applicant chooses to withdraw an application after the initial outcome has been issued (e.g. where an applicant chooses not to respond to requests for further information), the application should be set as not approved and an unfavourable opinion letter issued with the reason 'applicant decision to withdraw'.

Research not requiring review by a REC

1.80. Where an application is received by a REC, that does not require review by a REC within the UK Health Departments' Research Ethics Service under paragraph 2.3 of the REC Policy Document (including current legal requirements), the following procedures apply.

1.81. Research involving only staff of health or social care services, who are recruited by virtue of their professional role, and healthcare market research are generally excluded from the scope of REC review (see paragraphs 2.3.13 - 2.3.15 of the REC Policy Document) and should not normally be accepted. An application may, however, be reviewed exceptionally by a REC where the Research Ethics Service agrees that the proposal raises material ethical issues. Responsibility for deciding whether such research should be reviewed rests with an Operational Manager. Where a researcher or research sponsor wishes to apply to a REC, they are encouraged to seek advice in writing prior to completing an application. Market research may be undertaken by professional market researchers, e.g. for public health research or on behalf of pharmaceutical or medical device companies. Where such research is conducted by professional market researchers in accordance with the principles set out in the Market Research Society Code of Conduct or with the Legal and Ethical Guidelines issued by the British Healthcare Business Intelligence Association (BHBIA), it does not require REC review, except where otherwise required by law, e.g. if it requires approval under the Mental Capacity Acts within the UK.

1.82. Under paragraph 2.3.7 of the REC Policy Document, RECs may agree to consider applications in respect of activities preparatory to research (e.g. the establishment of

research databases or tissue banks, or pre-trial advertising and screening for healthy volunteers). Applications relating to the establishment of research tissue banks and research databases in the UK are voluntary but are welcomed by the Research Ethics Service. If a REC feels unable to review the application, arrangements should be made to transfer it to a REC able to review it. Requests for review of non-study specific pre-trial advertising and screening should be submitted to the Generic Document Review Committee.

1.83. Paragraph 2.3.7 of the REC Policy Document also allows a REC to review other research not requiring review under the policy and legal requirements set out in the REC Policy Document. Where such research involves human participants and raises material ethical issues, it is desirable as a matter of public policy that it is ethically reviewed. If the researcher does not have access to ethics review from another source, e.g. a university REC or an ethics committee established by a professional body, the REC may accept the application and give an ethics opinion on a voluntary basis. It is a matter for the HRA/UK RES to decide whether the application should be reviewed. Applicants are encouraged to seek the advice of the REC prior to completing the application. Where the HRA/UK RES agrees to review the application, it should be reviewed in accordance with standard operating procedures. Where the HRA/UK RES declines to review the application, the Operational Manager should decide whether or not to invite another REC to consider the application.

Advice on whether a project is research

1.84. Under the REC Policy Document, RECs are not expected to consider applications in respect of activities that are not research.

1.85. Within the NHS and social care services, the responsibility for determining whether a project should be managed as research lies with the responsible Research and Development office (R&D). Requests for pre-application advice should be referred initially to the R&D office, or a lead R&D office in the case of a project involving multiple organisations. The applicant or the R&D office itself may seek further advice using the HRA decision tools in the first instance and subsequently via the HRA Queries Line, should further clarification be required. On request to the HRA, REC Chairs may give informal advice, but a formal response should be sought via the HRA decision tools and, when required, the HRA Queries line.

1.86. Where an application is made to a REC, i.e. the project is presented as research, it should be validated and reviewed in the normal way if the research is within the scope of REC review under the REC Policy Document. If the REC considers that the

project should not have been presented as research, it may give advice alongside its opinion that the status of the project is reconsidered by the sponsor in consultation with the lead R&D office. If the sponsor or project team subsequently notifies the REC that the application is no longer considered to be research, the application and opinion letter should be withdrawn.

Retrospective applications

1.87. In some cases, applicants may disclose that the research has already started without first obtaining a favourable ethics opinion. For research within the health or social care responsibilities of the UK Health Departments, this is a breach of research governance. In the case of a CTIMP, a criminal offence may also have been committed. All such cases should therefore be reported to the HRA in accordance with the procedures for dealing with breaches which is published separately.

1.88. Such applications should be considered invalid, and the REC is not obliged to proceed with any form of ethics review. An ethics opinion cannot be given retrospectively. However, the REC has the discretion to consider the protocol and any other available documentation and to issue a letter to the applicant giving ethics advice about the project. The Chair may deal with the matter personally or the project may be considered at a full meeting of the REC or in sub-committee. If the REC considers the application is not research, the correspondence must make clear that the project must not be presented as research in the future. If the applicant terminates the research and then submits a valid application to start a new project, this may be reviewed in the normal way, taking account of any concerns about the suitability of the investigator.

1.89. On occasion, the HRA may receive queries or concerns from third parties relating to research that have not yet been submitted to REC (or CAG). Such concerns will be received by the HRA complaints group to manage such complaints. The group will consider the nature and range of the representations made and the Deputy Director of the Approvals Service will determine handling on a case-by-case basis. Where the third-party representations relate to a forthcoming application which is locally specific to a Devolved Administrations, information will be shared with appropriate equivalent postholders in the relevant nation.

Back to contents

Section 2: Full meetings of a Research Ethics Committee

General policy

2.1 All valid applications for an ethics opinion should be reviewed at a full meeting of a REC held in accordance with the following procedures, except where proportionate review procedures, or the expedited review process described in Section 9, apply.

2.2 Procedures relating to the outcome of the ethics review, including the decisions available at meetings and the request for further information or clarification following the meeting, are set out in Section 3.

Meeting schedules

2.3 A REC should normally hold at least 10 scheduled full meetings in each year for the purposes of the ethics review of applications. Additional meetings may be held where necessary to ensure that an ethics opinion on an application is given within the relevant time limit (see paragraphs 3.1-3.6), or to discuss matters relating to the establishment or operating procedures of the REC; or for training purposes.

2.4 Meetings to review applications should normally be held at intervals of one month. A longer interval is permissible when meetings span holiday periods but should not exceed two months where this can be avoided. Scheduled meetings may be cancelled with the agreement of an Operational Manager.

2.5 The meeting schedules of RECs should be appropriately staggered, in particular over the holiday periods, to ensure that it is possible for any valid applications to be reviewed within the relevant time limit.

2.6 The schedule of Committee meetings for the financial year commencing on 1 April should be agreed by 1 December in the previous financial year. The schedule should set out the dates and times of meetings, and the closing date for applications to each meeting. All members of the REC should be issued with details of the schedule.

2.7 The closing dates for full applications should normally be 14 calendar days prior to each REC meeting. Where the first meeting is refused, the clock will start on day 7. In the case of applications for Phase 1 clinical trials in healthy volunteers, RECs may adopt a later closing date for applications not less than 7 calendar days prior to the meeting and may accept applications booked in advance of the closing date which are submitted up to 7 calendar days before the date of the meeting. In the case of applications for Phase 1 clinical trials in healthy volunteers, RECs may adopt a later closing date for applications. If not less than 7 calendar days prior to the meeting and

may accept applications booked in advance of the closing date which are submitted up to 7 calendar days before the date of the meeting.

2.8 There may be proposed changes to the meeting schedules during the year. Any changes will be cascaded to the members of staff dealing with the REC and to the Chair/REC Members. The meeting dates will be updated on the HRA website and on HARP.

Agenda

2.9 An agenda should be prepared for the meeting. A standard format is available in HARP. The agenda should include at least the following:

- The date and time of the meeting.
- Confirmation of quoracy.
- Declarations of interest relating to items on the agenda (quoracy to be reconfirmed, where necessary, as per section 2.51 (i) and (ii)).
- Minutes of the previous REC meeting.
- Matters arising at the previous meeting(s) that the Committee specifically indicated that it wished to consider again.
- Applications for ethics review to be considered at the meeting.
- Lead reviewers for each application where applicable (see paragraphs 2.19–2.20).
- REC Report (see 2.13).

2.10 The agenda may also include reference to proposed discussion of the following where appropriate:

- General ethics issues, for example arising from new guidelines or recent publications
- Matters relating to the establishment or membership of the REC.
- Matters relating to REC procedures
- Training issues
- QC/QA reports
- Workload and decision-making data

2.11 It is important that REC meetings include sufficient applications to maintain the

expertise of the REC and justify the resources involved, but not so many as to undermine the rigour of the ethics review. The aim of the Research Ethics Service is that RECs should review around 3-4 new applications per meeting on average. Operational Managers will review the workload of RECs periodically.

2.12 Section 7 describes arrangements for REC business that may be conducted by sub-committees. The agenda for REC meetings may include items that would normally be reviewed in sub-committee, particularly where the Chair considers it important that a wider discussion takes place.

REC Report

2.13 Members should be notified in writing of business undertaken outside REC meetings, such as the following:

- Decisions or actions taken by the Chair, Vice Chair or Alternate Vice-Chair, or members under delegated authority (see paragraph 2.15) including decisions delegated to REC staff.
- Decisions taken by a sub-committee either at a meeting or in correspondence (the minutes of any appropriate sub-committee meetings may be appended to the REC Report or copied to members separately).Re
- Notification of the conclusion or early termination of research (see paragraph 10.66).
- Receipt of minor modifications.
- Receipt of final study reports (see paragraph 10.1119).

2.14 The report should be prepared for distribution to members with the documents for each meeting, using the template in HARP.

2.15 Where the REC has previously delegated authority to the Chair, named members or a sub-committee to issue its opinion following receipt of further information or clarification from the applicant (see paragraphs 3.31-3.33), it should be notified once the opinion has been issued. The following information should be provided in the report:

- The ethics opinion given on the application.
- The members that were involved in considering the further information.

2.16 Where an unfavourable opinion was given, it may be of interest to members to have a brief summary of the applicant's response, highlighting the points that failed to meet

the REC's requirements.

2.17 The REC Report should normally be distributed with the main documents for the meeting. Once the report has been finalised, any further business that takes place prior to the meeting may be deferred to the report for the following meeting. Where exceptionally the Chair or appropriate member of Approvals Staff/REC Manager considers it essential that a matter is reported to the REC as soon as possible, a further written report may be prepared, or a verbal update provided at the meeting.

2.18 The REC Report is mainly for the information of members and should not normally require detailed discussion. The decisions taken by the Chair, Vice Chair or Alternate Vice-Chair, or members on behalf of the REC, or by sub-committees or REC staff, do not need to be ratified by the REC. However, members should be allowed to raise any concern about the decisions taken on their behalf. Any such concerns should be considered by the REC and recorded in the minutes.

Lead reviewers

2.19 It is strongly recommended that RECs appoint one or more members as lead reviewers for each application for full applications in consultation with the Chair as necessary. A lead reviewer must also be appointed for each application to be reviewed by a proportionate review sub-committee. Use of the lead reviewer form is mandatory.

2.20 The specific role undertaken by lead reviewers both at the meeting and following the meeting is a matter for the discretion of the REC. Local procedures should be discussed and agreed by the members.

Distribution of documents for meetings

2.21 Documents for meeting should be made available as soon as possible after the agenda is finalised and applications have been validated, and in any case no later than 10 calendar days prior to the meeting (with the exception of expedited, Proportionate Review and Phase 1 applications where there has been prior agreement). Documents for the information of members may be distributed nearer to the date of the meeting or, exceptionally, tabled at the meeting. Under no circumstances should full applications be tabled at the meeting. Applications should be made available to members via the HARP member portal as soon as the application is validated, and an email sent to the members to inform them the application is now viewable.

Attendance of the Chief Investigator and sponsor

2.22 The Chief Investigator (CI) or delegated representative should be invited to attend the meeting. The sponsor's representative and other members of the research team are welcome to attend alongside the Chief Investigator. The purpose of this is to be available to respond directly to requests from the REC for further information, clarification or reassurance. In this way, any issues of concern to the REC may be resolved at the meeting. Even where further consideration needs to be given by the Chief Investigator and sponsor after the meeting to matters raised by the REC, their attendance to hear the points raised in person may well prove to have been helpful in formulating a satisfactory response.

2.23 It is, however, not compulsory for the Chief Investigator to attend, and consideration of the application should not be prejudiced if the CI is unable or unwilling to attend.

2.24 In the case of applications submitted by students, it should be strongly recommended that the academic supervisor attends the REC meeting

2.25 It is not the purpose of the Chief Investigator's attendance to make a formal presentation of the study, and this should not be permitted.

Quorum requirements and meeting attendance

2.26 Subject to paragraph 2.27, the quorum for meetings of a REC is five members, although it will always aim to have seven where possible. The REC meeting will include at least the following:

- A Chair person (this can be a Chair, Vice Chair or Alternate Vice Chair)
- At least one lay member
- At least one member with a healthcare designation. (For social care applications, this can be a member with a social care designation).

  The REC membership will collectively reflect the qualifications and experience to review the science, medical aspects and ethics of the research applications.

2.27 For applications relating to research with funding support from the US DHHS or one of its agencies, the quorum is a majority of the REC membership. Where the REC has an even number of members, a majority means 50% of the members plus one. All such applications should be reviewed by appropriately flagged RECs (see paragraph 1.7).

2.28 A co-opted member (see paragraphs 2.35-2.37) should also be counted for the

purpose of the quorum.

2.29 The following should not be counted for the purpose of the quorum:

- Approvals staff/REC Manager or REC Assistant.
- Advisers or referees.
- Members who are yet to arrive at the meeting, or who have left early.
- Members who submit written comments but do not attend. (see paragraph 2.41).
- Observers to the meeting.

2.30 Where a quorum is not present, the Committee may not give an ethics opinion on any new application for ethics review. The Committee may discuss the applications on the agenda and give preliminary advice to applicants, though it should not issue formal requests for information at this point. The ethics opinions of the applications will need to be agreed at a quorate meeting of the REC or transferred to another REC. The application clock does not stop.

2.31 A Committee meeting, or part of the meeting, at which a quorum of members is not present, may proceed with any other business on the agenda, provided that the Chair (or vice-Chair or alternate vice-Chair) and at least one other member is present.

2.32 A record of attendance should be kept indicating which were present for the discussion of each application for ethics review.

2.33 Where there is concern that a forthcoming meeting may not be attended by a quorum of members due to foreseen absences, staff should consider the following options in liaison with an Operational Manager:

- Co-opting additional members (see paragraphs 2.36 -2.38).
- Postponing and re-arranging the meeting.
- Cancelling the meeting; where it is proposed to cancel a planned meeting, agreement must be sought at an early stage.

2.34 If the meeting is postponed or cancelled, consideration should be taken to ensure that the applications listed on the agenda are processed within the statutory time limit. If necessary, the applications should be transferred to other RECs.

Co-opted members

2.35 A REC may co-opt additional members at any meeting of the REC for the purposes

of that meeting. A person may be co-opted as a member only if they are a member of another REC within the UK Health Departments' Research Ethics Service or a member of MoDREC.

2.36 In exceptional circumstances, a Chair, Vice Chair or Alternate Vice-Chair of a REC may be co-opted to Chair a meeting of a different REC. The appropriate indemnity for this should be arranged where applicable.

2.37 Procedures for co-opting members are the responsibility of the REC's appointing authority, acting on advice from and in accordance with guidance issued by the Head of Approvals Support and Improvement. Records of members should be maintained who would in principle be willing to be co-opted where required. All serving REC members are indemnified by their appointing authority for their actions as co-opted members of any REC.

Written comments from members

2.38 A member who is unavailable to attend a meeting may submit comments in writing on any agenda item. It is still acceptable for a deputy member to submit written comments if the lead member attends the REC meeting or also submits written comments. These should normally be entered in the HARP member portal prior to the meeting. The minutes should record that written comments were submitted from the member or deputy member concerned and reflect unattributably any specific points addressed by the REC in the ethics review.

2.39 A member or deputy member who submits written comments but does not attend the meeting does not count towards the quorum.

Referees

2.40 A REC may seek the advice of a referee on any aspects of an application that are relevant to the formation of an ethics opinion, and which lies beyond the expertise of the members or on which the Committee is unable to agree. These referees may be specialists in ethics, specific diseases or methodologies, or they may be representatives of communities, patients or special interest groups. Referees may be a member of another REC or an external referee with expertise in the relevant area. When providing expert advice as a referee REC members are not acting in their capacity as a member; the process for expert advice should therefore be followed.

2.41 Requests for expert referee advice should be addressed via the Approvals Specialist/REC Manager of the REC concerned.

2.42 Referees are not voting members of the REC and should not be involved in the business of the REC other than that related to the application on which their advice is sought.

2.43 The advice of a referee should be sought using one of the following procedures:

(a) The Approvals Specialist/REC Manager or Chair may write to the referee seeking written advice prior to the meeting, but where the REC has a regular arrangement with a particular referee a suitable alternative may be used. A copy of the advice received should be made available to members prior to the meeting or tabled at the meeting. The substance of the advice should be recorded in the minutes.

(b) The referee may be invited to attend the meeting to discuss the application concerned. The attendance of the referee and the substance of their advice at the meeting should be recorded in the minutes. The referee should not personally question the Chief Investigator at the meeting, or have a vote in the ethics decision taken by the REC.

(c) The Committee may decide at the meeting to seek written advice following the meeting. The Approvals Specialist/REC Manager or Chair should email the referee within 7 calendar days of the meeting using the template available in HARP. The written advice received should then be considered promptly in accordance with procedures agreed at the meeting (see paragraphs 3.41-3.45 for further guidance).

2.44 The application clock for the ethics review does not stop while the advice of a referee is sought, only once a written request for further information is made to the Chief Investigator.

2.45 Referees should be required to treat in confidence all information provided about the application, except where already in the public domain, and to return or destroy any application documentation. Documents should not be shared with the referee until there is agreement from the referee that they will review the application. When a referee is approached to provide specialist advice, the advice given should be recorded in the minutes as given by a referee but not attributed to the referee by name or designation. The Approvals Specialist/REC Manager should also record what the Committee decided to do when taking the advice into consideration. When specialist advice is requested after the REC meeting, prior to a decision being given, the advice provided should be reviewed by a sub-committee of the REC. This guidance for full REC minutes should be replicated for sub-committee minutes.

2.46 The ethics opinion reached by the REC on an application is its own. It may draw on the referee's advice in framing its opinion, including any request for further information, and may indicate to the applicant that it has sought advice from a referee. However, it should not cite the referee directly or otherwise disclose the referee's identity in the ethics opinion correspondence except with his/her express permission. The original correspondence and any reports from a referee should be retained in HARP for subsequent reference where necessary (see section 15).

Declarations of interest

2.47 Members should declare to the Committee any material interests they may have in relation to an application for ethics review or any other matter for consideration at that meeting. Such a declaration may be made verbally at the meeting, prior to the matter being considered, or in writing to the Chair prior to the meeting. All members present should be aware of which individual declared the interest, what the declaration of interest was and should take account of the closeness of the member's interest in the application. A material interest is any personal or business interest that may, or may be perceived to, unduly influence the member's or the Committee's judgement about the matter concerned.

Applications for ethics review

2.48 Subject to paragraph 2.51, where the member concerned is the Chief Investigator (CI), another key investigator/collaborator or the sponsor representative named on the application form, the REC should not proceed with the review, and arrangements should be made urgently for the application to be transferred to another REC. The only exceptions to this are for CTIMPs involving adults with incapacity taking place in Scotland where the CI is professionally based in Scotland and non CTIMPs involving adults with incapacity taking place in Scotland. These studies must be reviewed by a designated REC in Scotland and therefore local procedures apply.

2.49 In the case of any other declared interest, the Committee should collectively consider whether it is a material interest and, if so, whether it is appropriate for the member concerned to take any part in the review of the application. Account should be taken of the closeness of the member's interest in the application and the potential for a conflict of interest. There is no need to record any declarations which the Committee decided was not material in the minutes of the meeting. In some cases, the

declaration of the interest may in itself be sufficient to ensure that the decision of the Committee is not unduly influenced.

2.50 The minutes should record any declaration of interest the Committee considers to be material, and its decision on the procedure to be followed. If the Committee is in any doubt, it is recommended that the member should leave the meeting as in paragraph 2.51.

2.51 The Committee has the following options:

(i) The member should leave the meeting and take no part in the discussion or the vote on the application.

(ii) The member may remain in the meeting in order to provide any relevant information requested by other members but may not vote.

(iii) The member may remain in the meeting and take a full part in the review.

Confidentiality of proceedings

2.52 REC members do not sit on the Committee in any representative capacity and need to be able to discuss freely the applications submitted to them. For this reason, REC meetings should be held in private, and members should be encouraged to raise any matters of concern.

2.53 The terms and conditions of appointment for members include requirements to keep confidential the business of the REC.

2.54 REC Members should delete any saved electronic copies of documents after a final ethics opinion has been issued.

Observers

2.55 Each REC will have internal and external observers joining their meetings, subject to the clauses below. Internal staff who join as observers will be doing so in an official capacity, either as part of their induction, as part of their role or in order to undertake observations that contribute to the quality assurance of the service. External observers will come from a range of backgrounds including members of the public, people working in research in the NHS or industry or individuals who wish to join as a REC members.

2.56 External observers may be invited to attend REC meetings, subject to written invitation setting out the terms under which observer status is permitted, the signature of a confidentiality agreement, and the agreement of the REC at the meeting to be

attended. Confidentiality agreements should be drawn up using the model form available in SharePoint and the signed copy should be uploaded to the meeting documents tab in HARP. The agenda may be shared with the observer; however, the application and supporting documentation cannot be shared due to confidentiality reasons.

2.57 External observers should have no vested interest in any applications being considered at the meeting. Where an observer does have a vested interest in an application being reviewed at the meeting, the observer should inform the REC of this. R&D Directors and R&D managers should not generally be permitted to attend meetings of RECs at which applications for which they have research governance responsibilities are to be reviewed. However, where an NHS body is sponsoring the research, an R&D representative may attend the meeting for that item only alongside the Chief Investigator. In such cases, the R&D representative attends as the research sponsor, in accordance with paragraph 2.22 rather than as an observer.

2.58 Meetings, or parts of meetings, may also be attended from time to time by staff, auditors, and other senior staff from the appointing authority in accordance with governance arrangements for RECs ("official observers"). The Chair should be notified prior to the meeting.

2.59 Observers should take no part in the REC's deliberations or ethics decisions as part of the applications ethics review. However, 'official observers' (see 2.55 for description) may provide operational advice to the REC.

2.60 If any observer is present, the Chair should verbally inform any study representative who attends the meeting. The attending study representative should be given the opportunity to object to the presence of an observer (other than an official observer). If there is an objection, the observer should be asked to leave the meeting for that item. The attendance of observers should be recorded in the minutes.

Conduct of business and decision-making

2.61 The Chair is responsible for the conduct of the business and for ensuring that the Committee reaches clearly agreed decisions on all matters. Where the Chair is unavailable, the meeting should normally be chaired by the vice-Chair or, if the vice-Chair is also unavailable, by the alternate vice-Chair. If all three are unavailable, A Chair, Vice Chair or Alternate Vice-Chair of a different REC may be co-opted to Chair the meeting in agreement with the Operational Manager, this applies to both full and Proportionate Review meetings.

2.62 The Chair should have regard to RES operational guidance on the conduct of meetings and ensure that members use the lead reviewer checklist.

2.63 Vice-chairs should chair at least one meeting per year when the Chair is present for training purposes. When doing so, they carry the normal responsibilities of the Chair.

2.64 The meeting should reach unanimous decisions by consensus wherever possible. Where a consensus is not achievable a formal vote should be taken by a counting of hands. The decision of the Committee should be determined by a simple majority of those members present and entitled to vote. A record should be kept of the number of votes, including abstentions, in the minutes. Where the vote is tied, the Chair may give a casting vote, but should first consider any other options to arrive at a more consensual decision.

2.65 Where any member wishes to record his/her formal dissent from the decision of the Committee, this should be recorded in the minutes but should not be included in the opinion letter.

Responsibilities of Staff

2.66 The responsibilities of the staff in relation to REC meetings are as follows:

- Publishing the schedule of REC meetings.
- Preparing the agenda.
- Allocating lead and second reviewers.
- Making the agenda and documents on the HARP Reviewer Portal.
- Inviting Chief Investigators and, where appropriate, supervisors to attend and making the necessary arrangements.
- Recording apologies for absence prior to the meeting.
- Recording the attendance of members, referees and observers.
- Advising the members as necessary on compliance with standard operating procedures and, where relevant, the need for the REC to consider legal requirements applying to the ethics review (e.g. the criteria for approval under the UK Mental Capacity Acts).
- Providing guidance to members if inappropriate issues are raised during the meeting and advising members on the correct use of ethics opinions.
- Making a written record of the meeting.

- Recording individual votes where a vote is taken on a decision (e.g. 12 for / 3 against).
- Preparing the minutes of the meeting within 2 working days and obtaining subsequent approval at the following meeting.
- Notifying applicants of the ethics opinion taken at the meeting and taking other follow-up actions, as necessary.
- Recording any material Declaration of Interests (DOI) and subsequent actions.
- Check the meeting is quorate throughout its duration

Minutes

2.67 The minutes of the REC meeting should be prepared by the relevant members of staff.

2.68 In relation to applications for ethics review, the minutes should contain a record of the following for each study, whether in the main text of the minutes or in attachments:

- The members, co-opted members, referees and observers present for the review.
- Any material interests declared, and the decision of the Committee on the participation of the member or deputy member concerned (see paragraphs 2.48-2.51).
- The submission of written comments by members or deputy members, detailing the relevant REC reference number (see paragraph 2.38)
- The substance of any advice given by a referee (see paragraph 2.46).
- The decision of the REC on the application (see paragraph 3.7).
- A summary of the main ethics issues considered (see paragraph 3.11 – 3.12).
- In the case of a favourable opinion, any conditions to be met prior to the start of the study or additional non-binding advice to be given to the applicant (see paragraphs 3.16- 3.27).
- In the case of an unfavourable opinion, the predominant reasons for the decision are clearly stated and are distinguished from other comments or advice suggested by the REC. In the case of a provisional opinion,

the further information requested by the REC and the arrangements for considering the information and issuing the final opinion of the REC are clearly noted (see paragraph 3.26).

- Where an unfavourable opinion is given on a substantial modification, the reasons for the decision
- The outcome of any vote taken.
- Any formal dissent from the decision of the REC by a named member, with reasons.
- Whether an application was reviewed on a voluntary basis rather than as a requirement of policy or legislation (see 1.83).

2.69 The minutes should be presented as the outcome of collective discussion and should not attribute particular statements to individual members attending the meeting or providing written comments. The minutes of the meeting should be written in the third person and should contain an accurate record of what was discussed during the meeting. Verbatim comments should not be included in the minutes. Good practice examples of minutes are available on the SharePoint.

2.70 A draft version of the minutes should be provided to the Chair (and the Approvals Specialist in England and Wales) within 2 working days of the meeting. The Chair (and the Approvals Specialist in England and Wales) should check them within 3 working days. Draft minutes (watermarked ‘management in confidence’) should be uploaded to HARP. Once reviewed, any requested changes should be made, although these should be minimal. When ratified, the final signed minutes (in PDF format) must be uploaded to HARP. They should be signed and dated by the Chair and by the Approvals Administrator/REC Manager or REC Assistant. Electronic signatures are acceptable if the email from the Chair attaching the signed minutes is also uploaded. Once the ratified minutes are uploaded, the draft version should be deleted from HARP.

2.71 The minutes should also be submitted to the following meeting of the REC. If at the subsequent REC meeting, any requests for changes are made, the Chair should consider whether, if the revisions are minor, any updates are needed to the final version of the minutes, or whether these can be noted in the minutes of the subsequent meeting. Any necessary revisions should be incorporated in the final version of the minutes, which should be re-signed by the Chair and staff and the revised minutes uploaded to HARP when the changes have been incorporated.

Where significant revisions are made to the minutes, it should be considered whether applicants should be informed about any inaccuracies contained in the outcome which was sent to them after the meeting. However, no substantially new requests for information may be made at this point.

2.72 Subject to the provisions of the Freedom of Information Act, the minutes should be treated as confidential to the REC and not routinely disclosed to applicants, sponsors or care organisations. For guidance on retention of minutes, see paragraph 15.8. The opinion of the REC on each application for ethics review should be published on the HRA website.

Back to Contents

Section 3: Giving an ethics opinion

Statutory and policy requirements

3.1 Under the Clinical Trials Regulations, a REC is required to give an initial ethics opinion on an application relating to a CTIMP (except where paragraph 3.2 applies) within 30 calendar days of the receipt of a valid application. Where the REC considers that further information is required in order to give an opinion, the REC may issue a Request for Further Information (RFI and make one request in writing for further information from the applicant. A final ethical opinion following receipt of a Request for Further Information should be issued within 10 days.

3.2 For some applications, the REC or MHRA may need independent expert advice from a specialist group or committee. In these cases, the timeframes for the approval process may be extended to allow for the advice to be requested and received – see 3.45 for more details. For CTIMPs involving xenogenic cell therapy, the timeframes outlined in paragraph 3.1 do not apply - outcomes and decisions can be issued at any point after an application is received and validated. Except for this difference in the time limit for review, SOPs apply to such trials in the same way as any other CTIMP.

3.3 Under the Clinical Trials Regulations, the REC has a duty to consider and give an opinion on any issue relating to a CTIMP if it has been asked by the applicant to do so and, in the opinion of the REC, it is relevant to matters the REC is required to consider as part of the ethics review.

3.4 The policy of the UK Health Departments is that a maximum 60 calendar day time limit will also apply to all other research reviewed at a full meeting of a REC.

3.5 For applications accepted for proportionate review, the final opinion should be given within 21 calendar days, allowing for the clock to stop once where a request for information is issued.

3.6 Guidance on the matters to be considered in the ethics review of research and training for REC members are provided separately by RES. This section of the SOPs sets out the procedures to be followed in communicating decisions made at meetings, requesting further information from applicants and issuing the REC's opinion. It does not in any way constrain the independence of the REC in considering the ethics of individual research applications and deciding whether or not to give a favourable opinion.

Decisions available to the REC

3.7 A REC should reach one of the following decisions on any application reviewed at a full meeting or a proportionate review sub-committee meeting:

a) Final opinion

The Committee may reach one of the following final opinions on the application:

- favourable opinion with standard conditions (see paragraph 3.16),
- favourable opinion with additional conditions (see paragraph 3.24),
- unfavourable opinion (This is an option for non-CTIMPs only. For CTIMPs, an unfavourable opinion can only be issued following a request for further information in the first instance)

b) Request for further information

Where necessary, the REC can issue a request for further information. For CTIMPs, where the REC cannot issue a favourable opinion (with or without additional conditions), it will issue a request for further information in the first instance (see paragraph 3.31). Following a response to the request for further information, the Committee will then issue a final opinion.

c) Request for further information pending consultation with referee

A full meeting may decide that a final opinion cannot be issued until further advice has been sought from a referee (see paragraphs 3.41 - 3.45). A formal request for further information would be issued following advice from the referee. For CTIMPs, this would occur within the 30 calendar day review period.

3.8 The Approvals Administrator/REC Manager should ensure that the minutes clearly record the decisions taken by the REC, any further information requested from applicants and the agreed procedures for considering that information and issuing the REC's opinion.

3.9 The decision taken on each application should be entered on HARP.

Notification of the decision to the Chief Investigator

3.10 Notification of the decision should be sent to the sponsor and/or individual delegated by the sponsor, and for non-CTIMPs, the Chief Investigator (CI). Notification will be sent within at least 14 calendar days of a full meeting (preferably fewer), or within 7

calendar days of a proportionate review meeting. For CTIMPs, the initial outcome should be issued in HARP within 28 calendar days of confirmation of a valid application to allow a period of consolidation with the MHRA. The outcome will be shared with the applicant by email within a maximum of 30 calendar days following confirmation of a valid application. For CTIMPs if the REC is unable to issue a favourable opinion (with or without additional conditions), or for non-CTIMPs where it is decided that more information is needed before issuing an opinion, the REC will send the sponsor a request for further information. Where the REC sends a request for further information, the sponsor has 60 calendar days to respond. If required, the sponsor can request an extension. Following receipt of the response, an outcome should be sent to the sponsor within 10 calendar days (see 3.31 for more details on requests for further information). In the case of projects undertaken primarily for educational purposes, the decision outcome and all further correspondence should be addressed to the student (or the first named student on the application if more than one is involved) and copied to the CI if different. All letters should be in the name of the Chair of the REC, it is acceptable for the letter to be signed by a vice-Chair or member of staff supporting the REC acting under delegated authority from the Chair. The following letters or emails are available.

a) Applications reviewed at a full meeting:

- Favourable opinion (with standard conditions or additional conditions)
- Unfavourable opinion
- Request for further information (for CTIMPs requests for further information are released via HARP).
- Request for information pending consultation with a referee.

b) Applications reviewed by sub-committee under proportionate review:

- Favourable opinion (with standard conditions or additional conditions)
- Unfavourable opinion
- No opinion – application referred to full meeting

3.11 The following information should in all cases be included in the decision outcome:

- A list of all documents reviewed at the meeting, giving correct version numbers and dates.

- A list of the members who were present for the discussion of the application or who submitted written comments on the application prior to the meeting.
- Declarations of interest by members, which were material to the application, and whether or not the member concerned took part in the review and voted on the decision (it is not necessary to give details of the interests, only that a declaration was made). This will be included on the Request for Information status update or final opinion letter (if an outright Favourable Opinion or Unfavourable Opinion is issued).
- The names of any observers present at the meeting.
- The detail of any requests for further information required from the applicant, including an explanation of the reasons based on the RECs discussion, before the final opinion can be issued or any conditions of the favourable opinion, this will be confirmed on the final opinion letter. In some cases, the absence of version numbers and dates should be raised with the applicant. Additionally, in the case of favourable opinion, a list of all documents which received a favourable opinion giving correct version numbers and dates. Where an unfavourable opinion is issued, a list of all documents reviewed at the meeting will be included.

3.12 The letter should also include the REC's opinion on any relevant issue on which the applicant has specifically asked for its opinion (see paragraph 3.3).

3.13 The letter should not attribute particular comments or questions to individual members of the REC.

Final opinion letters

3.14 All letters issuing the REC's final opinion should be in the name of the Chair of the Committee (or chair of the sub-committee in the case of proportionate review), it is acceptable for the letter to be signed by a vice-chair or a member of staff supporting the REC acting under delegated authority from the Chair. The letter should be emailed to the applicant within the relevant time limit for review of the application (see paragraphs 3.1- 3.4).

3.15 The opinion of the REC should be entered on HARP. The date of the opinion is the date on which the final opinion letter is sent. For CTIMPs, the date of the opinion is the date the UK final opinion is issued to the applicant.

Favourable opinion

3.16 When giving a favourable opinion, the REC may specify any conditions to be met prior to the start of the study (or the start at each location). These should be clearly set out in the favourable opinion letter. The conditions must be met in order for the favourable opinion to be in place once the study starts; until they are met, the study does not have a favourable opinion and should not start. It is the responsibility of the sponsor to ensure that the specified conditions are met. For CTIMPs, additional conditions should be issued as a request for further information prior to confirmation of a final favourable opinion.

3.17 A standard condition of any favourable opinion is that the sponsor must obtain management permission or approval from relevant host organisations prior to the start of the study at each location. The favourable opinion therefore applies to all NHS locations on condition that NHS management permission is confirmed prior to the start of the study at that location.

3.18 In addition, where a study requires any kind of regulatory approval under legislation (e.g. from the MHRA), it is a standard condition that the sponsor should obtain such approval prior to the start of the study.

Transparency Requirements

3.19 With the exception of student research, all studies are expected to meet transparency requirements across the following areas, applicable to the study type:

a) Registration

For CTIMPs, it is a legal requirement as per the Clinical Trial Regulations to register the study on a public register before recruitment of the first participant or within 90 days of approval of the study, whichever is sooner – not doing so would be an offence. For all clinical trials, this is a condition of the REC favourable opinion. For other types of research (except student studies), it is expected that research should be registered on a publicly accessible database before it starts.

b) Publication of results

For CTIMPs, results must be published within 12 months of the end of the study on the public register or registries where the study is registered. This is a legal requirement as per the Clinical Trial Regulations and not doing so would be an offence. For other types of research (except student studies), it is expected that findings, whether positive or negative, are made publicly accessible in a timely manner after the research has finished.

c) Sharing of results

For CTIMPs, the results of the research must be offered to all participants and/or relevant persons in a manner that is understandable to lay people. This is a legal requirement as per the Clinical Trial Regulations. For all other types of research (except student studies), it is expected that results are made available, in a suitable format and timely manner, to those who took part in it, unless otherwise justified.

d) Sharing data and tissue

Where possible, it is recommended that data and any tissue collected for research are made accessible with appropriate safeguards.

For all research with a REC opinion, the HRA will publish a research summary on their website (see paragraph 3.55),

3.20 For CTIMPs, unless an appropriate deferral or waiver is in place, failure to comply with the requirements to register or publish a summary of results will constitute an offence under the Clinical Trial Regulations and, if not rectified, may result in action being taken by the MHRA. The HRA will work with the MHRA to support compliance monitoring.

Deferral of transparency requirements

3.21 In some cases a sponsor may need to defer transparency activities, for example, to protect confidential commercial information. In these cases, a sponsor can request a deferral to the timeframes of the transparency activity or activities. The publication of the research summary on the HRA website can also be deferred.

3.22 For CTIMPs, the sponsor can request a deferral of transparency requirements by stating this in the relevant question in the 'study information' section of the application. For other studies, or for CTIMPs where a deferral is requested after the application has been submitted, the sponsor can request a deferral by emailing deferrals@hra.nhs.uk. The HRA website provides more information about the deferrals policy and process.

3.23 Phase 1 CTIMPs involving only healthy volunteers will be automatically deferred for all transparency requirements. Confirmation that a deferral is in place for these trials will be provided as part of the final approval given to a trial.

3.24 Examples of other conditions to be met prior to the start of the study (or the start at each location) might include:

- Specific additions or modifications to the participant information sheet or other

study documentation.

- Ensuring that investigators and other research staff have been trained to undertake interventions or procedures outside their routine competence.
- Reaching agreement with the responsible care organisation(s) on responsibilities for funding the plan for continuing care of participants at the end of the study.
- Ensuring data encryption is in place on the PCs or laptops to be used in the research.
- For Phase 1 studies in healthy volunteers, participants must be registered on 'The Over-Volunteering Prevention System' (TOPS). All relevant fields must be completed when the participant is registered, and the system should be updated as appropriate for each participant on an ongoing basis.

3.25 The REC should not attach conditions where:

- The changes concerned would require further ethical consideration in order for the REC to give a favourable opinion of the research (e.g. significant and unspecified revision of the participant information sheet); or
- They relate to changes to be made to the conduct of the study after it has started.

Such issues should be fully addressed during the ethics review and where appropriate reflected in revisions to the protocol or other study documentation before the final opinion is given. If the REC is unable to issue a favourable opinion based on the application and any further information or clarification supplied by the applicant in the course of the review, an unfavourable opinion should be given.

3.26 The Chief Investigator or sponsor should notify the REC for information in writing once the conditions have been met (except for management permission or approval at individual locations) and provide copies of final documentation for reference purposes where appropriate. Receipt should be acknowledged within 7 calendar days and giving a complete list of the final documentation approved for the study.

3.27 The REC may also give advice or make suggestions that are not binding on the applicant. These should be clearly distinguished from any conditions specified as part of the favourable opinion. The REC should only include non-binding advice or suggestions where these are not material to the ethics opinion, i.e. it would not change the REC's favourable opinion of the research if the applicant opted not to

implement them. Where any changes suggested would amount to substantial modifications (e.g. to the study design), the applicant should be advised of the need to notify the REC and obtain a favourable opinion before implementing them.

Unfavourable opinion

3.28 Where the final opinion is unfavourable, the applicant should be given a full explanation of the REC's reasons, clearly separated from any suggestions or comments made by the REC. The applicant should also be informed of the options available for further review (see Section 8).

3.29 In a CTIMP or a clinical investigation of a medical device, the REC should discuss with the MHRA before issuing an unfavourable opinion related to topics that fall within MHRA Part 1 Assessment. Where the REC is minded to give an unfavourable opinion on such grounds, it should request further information in the first instance, enabling the sponsor to provide further information addressing these points and consult the MHRA in parallel. Procedures for consulting MHRA are set out in Section 14. For CTIMPs, the REC should issue the reasons why a favourable opinion cannot be issued as a request for further information. The applicant is permitted to respond prior to the REC confirming the final opinion which may be unfavourable.

3.30 Where a REC has given an unfavourable opinion on an application for ethics review (for CTIMPs this would always be following a request for information), the applicant has the following options for seeking further review:

a) The applicant may submit another application, which should be reviewed as a new application (paragraphs 8.2 - 8.8);

b) The applicant may appeal against the decision of the first REC and seek a second opinion from another REC on the same application ("the second REC") (paragraphs 8.11).

c) Request may be made to vary the opinion where it appears to be based on error or misunderstanding (see paragraphs 3.51 - 3.55).

Request for further information

Delegation of responsibility

3.31 Where the Committee or sub-committee requests further information from the applicant, it should decide in the initial review the procedures for considering that information and determining the REC's final opinion. This also applies to consolidation with the MHRA for CTIMPs. These responsibilities should normally be delegated to one of the following:

a) Designated REC supporting staff (e.g. Approvals Specialist/REC Manager)

b) the Chair, Vice Chair or Alternate Vice-Chair of the reviewing committee alone

c) The Chair, Vice Chair or Alternate Vice-Chair of the reviewing committee and the designated lead reviewer for the study

d) Chair or vice-chair, in oral or written consultation with one or more named members that were present at the meeting or who submitted written comments on the application, or with a REC Manager/Approvals Specialist or Operational Manager.

e) Exceptionally, a Sub-committee involving named members.

In deciding the procedures to be followed, the Committee or sub-committee should consider the significance of the further information and the expertise necessary to assess it. If the information is purely administrative or very straightforward, for example minor corrections to the participant information sheet, RECs are encouraged to delegate responsibility to a member of staff supporting the REC. Where the information is technical, or any questions of judgement are likely to arise, the Chair or Vice-Chair should personally review the information. Consideration should be given to involving other members where appropriate, such as the lead reviewer or a relevant expert member, or a Scientific Officer to the Committee. Where these questions are likely to be significant, a sub-committee should be appointed so that they can be fully discussed.

3.32 Where responsibilities for review of information are delegated to the lead reviewer, Scientific Officer or REC supporting staff, the Chair of the Committee or sub-committee remains ultimately accountable for the opinion.

3.33 Exceptionally, the REC may decide that the information should be considered at a further meeting of the REC. When taking this course, the REC should take careful account of the relevant time limit and the fact that the applicant is under no obligation to provide the information by a specified date, provided that it is received within a period of two months. If the information is received following the closing date for submitting papers to a scheduled meeting of the REC, it could therefore be necessary to arrange an additional meeting.

Suspension of the clock

3.34 The application clock should be suspended from the date on which the request for further information was sent to the applicant (for CTIMPs, the clock should be suspended on the date the Part 1 & Part 2 outcomes are submitted in HARP). It should be re-started on the date when a complete response is received (“the re-start

date").

3.35 Where the response arrives piecemeal, the re-start date is the date on which the final part of the response is received.

3.36 The re-start date is the date on which a complete response is received and not the date on which the information is considered by the REC and judged to be acceptable or otherwise.

Requirement for a complete response

3.37 If the applicant's response is incomplete or does not appear to fully address the matters raised, the REC is entitled to insist on a complete response before issuing its final opinion. The appropriate member of Approvals staff/REC Manager should write to the applicant (issued as a request for further information clarification via HARP for CTIMPs), setting out the further information or clarification still required (the letter may be issued more than once if the response continues to be incomplete). It is recommended that the applicant is contacted to discuss the outstanding points and clarify what is expected. The REC is not entitled to raise any new issues or concerns at this stage of the process. The clock should remain suspended until a complete response is received from the applicant.

3.38 The applicant should normally be allowed a period of 60 calendar days to respond to the request for further information (the timeframe is the same for CTIMPs). If no response is received within 60 calendar days, the REC will issue an unfavourable opinion (see paragraph 3.40 for details on final opinion following consideration of the information). The applicant would then be required to submit a new application in order to obtain an ethics opinion. However, the Approvals staff/REC Manager may extend the 60 calendar day period at the request of the applicant where there are reasonable grounds for requiring more time to respond. For CTIMPs, requests for an extension should be sent to the MHRA unless the points raised only relate to REC review, in that case the REC should be contacted directly. In their request, the sponsor should include an explanation as to why they need an extension and when they expect to respond. If an extension is agreed, then the REC and MHRA will make each other aware of this. If a request for an extension is not made (or agreed) and the sponsor does not submit a response within 60 calendar days, the MHRA will treat the application as rejected and the REC will issue an unfavourable opinion (see paragraph 3.40 for details on final opinion following consideration of the information).

3.39 The response to the Committee's request for further information should be provided by the Chief Investigator. It may include information supplied by a representative of

the sponsor, or by other key investigators or collaborators, but should always be assured by the Chief Investigator.

Final opinion following consideration of the information

3.40 On receipt of a complete response from the applicant, the REC should issue its final opinion on the application, which may be favourable, favourable with additional conditions or unfavourable. An outcome will be given to the applicant within a maximum of 10 calendar days. The 10 day timeline will not begin until a complete response is received. The procedures set out in paragraph 3.10 should be followed. One of the following will be communicated:

- Favourable opinion following consideration of further information
- Favourable opinion with additional conditions following consideration of further information
- Unfavourable opinion following consideration of further information

Further advice from a referee

3.41 Where a full meeting of a REC decides that it cannot give a final opinion until it has obtained further advice from a referee, it should inform the applicant in the first instance. The letter will explain that the REC will be consulting a referee and will write to the applicant again either to give a final opinion or to make a formal request for further information. The letter should summarise the discussion at the meeting and indicate the areas of concern raised by the REC. However, it should not request any response from the applicant at this point. **The clock does not stop as a request for further information has not yet been issued.**

3.42 In some cases, the REC may decide at the meeting it wishes to consult a referee. If so, this decision and the area of expertise required should be recorded in the minutes. If not, either the Chair or the Approvals Specialist/REC Manager should be appointed to identify a suitable referee urgently following the meeting. The referee may be another REC member or an expert in the specialist field.

3.43 The Chair or Approvals Specialist/REC Manager should initially contact the prospective referee to establish whether they are willing and able to provide expert advice within the required timescale. It should be established that the prospective referee has no connection with the research that might give rise to a conflict of interest. Advice should be given about confidentiality (see paragraph 2.46).

3.44 When advice is being sought from a referee, the Approvals Specialist/REC Manager

should email the referee using the template available on SharePoint. The request should be as specific as possible about the issues of concern to the REC and the expert advice required. A copy of the application form should be provided, together with any supporting documentation required by the referee. Where possible, the letter should be sent within 7 calendar days of the meeting. The referee should be asked to respond in writing within a further 14 calendar days.

3.45 Once the referee's advice has been received it should be considered promptly by a sub-committee of specified members (as determined at the full REC meeting). It may be decided to request to the applicant for further information or clarification at this point, taking into account the advice of the referee. The clock stops at this point. The procedures in paragraphs 3.31 apply to further review and issue of the final opinion following the response from the applicant. The applicant should be informed where a final opinion can be reached as a result of the referee's advice.

Independent Expert Advice (for CTIMPs only)

3.46 For CTIMPs, there may be occasions where the REC or MHRA need independent expert advice from a specialist group or committee (see statutory definitions section for a description of these groups and committees as defined in the Clinical Trial Regulations). When independent expert advice is needed, it will be sought during the initial review of an application and/or after receiving a response to a request for further information. The timeframes for the approval process may be extended to allow for the advice to be requested and received. If independent expert advice is sought:

- during the initial review of an application, then the 30 day timeframe may be extended by up to an additional 90 calendar days (bringing the maximum timeframe to 120 calendar days)
- following a response to a request for information, then the 10-day timeframe may be extended by up to an additional 30 calendar days (bringing the maximum timeframe to 40 calendar days)
- following a response to a request for information where an Advanced Therapy Medicinal Product (ATMP) is involved in the trial, then the 10-day timeframe may be extended by up to an additional 60 calendar days (bringing the maximum timeframe to 70 calendar days)

If the REC or MHRA determine that they need to seek independent expert advice, they'll notify sponsors that this is happening, ask for any additional information needed to allow

this, and let the sponsor know when they can expect to receive the outcome.

Regulatory approval

3.47 It is the responsibility of the sponsor to ensure, where necessary, that a research study has appropriate regulatory approval as well as a favourable ethics opinion before it starts. Guidance on other regulatory approvals, and communications between RECs and other bodies during the review process, is set out in Section 14.

Insurance, indemnity and compensation

3.48 Before confirming a favourable opinion on any research (including both CTIMPs and non-CTIMPs), the REC should assure itself that the sponsor and investigators will have appropriate insurance or indemnity cover for the potential legal liability arising from the research, and consider provision in proportion to the risk for compensation or treatment in the event of injury, disability or death attributable to participation. Detailed guidance is in Annex D.

Notifying other bodies of the progress of applications

3.49 It is the responsibility of the Chief Investigator to inform other interested bodies of the progress of the ethics review. The REC is not accountable for ensuring that bodies such as the sponsor, funder and relevant care organisations are kept informed and provided with copies of any documentation required. However, the REC should take reasonable steps to facilitate good communication between those concerned.

3.50 Standard procedures for the copying of correspondence are as follows:

a) The REC should send the sponsor's representative a copy of all letters to the Chief Investigator about the progress of the application, and any subsequent correspondence about the study following issue of a favourable opinion. Where more than one sponsor has been named on the application, correspondence will be sent only to the sponsor nominated to take responsibility for communications with the REC.

b) The Chief Investigator and sponsor will be expected to arrange for other care organisations to be kept informed and in particular to receive copies of letters from the REC confirming the favourable opinion for the study and for the location.

c) Procedures for communicating with other regulatory bodies during initial review and following the start of a study are set out in Section 14.

Variation of the opinion

3.51 Where a REC has given an opinion and subsequently receives information suggesting that the opinion is based on a factual error or misunderstanding, it may vary its opinion. This could apply, for example, where there has been an error or misunderstanding in relation to the application or the further information provided by the applicant or advice from a referee;

a) interpretation of relevant legal or regulatory requirement

b) the application of other published guidance to the conduct or management of the study

3.52 An unfavourable opinion may be varied to a favourable opinion or to a request for further information where the reasons for the opinion no longer apply
A favourable opinion may be varied by issuing a new unfavourable opinion letter clarifying the terms of the opinion. The need for this might arise where the study would otherwise be in breach of law, regulation or other recognised good practice, or it is not reasonably practicable to comply with the changes requested by the REC as part of a request for further information or the conditions attached to the final opinion.

3.53 A variation of the opinion may be requested by the Chief Investigator or sponsor by writing to the REC, copied to the Head of Approvals Operations. A variation may also be requested by the Head of Approvals Operations after consultation with the CI and sponsor.

3.54 Requests to vary the opinion should be considered by the Chair and other members as appropriate and a decision communicated to the Chief Investigator within 35 calendar days of receipt of the request. Where the opinion is varied, the Approvals staff/REC Manager should issue a new version of the final opinion letter. The letter should state that the previous opinion is superseded by this opinion and explain how the opinion has been varied, for example by confirming the REC's agreement to relevant points, withdrawing previous requests or amending the approval conditions.

3.55 In rare circumstances, an applicant may dispute or be unable to comply with the additional conditions of a favourable opinion. The Medicines for Human Use (Clinical Trial) (Amendment) Regulations 2025 do not make provision to appeal decisions other than for an unfavourable opinion. However, it is RES policy that requests to appeal decisions other than unfavourable opinions will be considered Requests to appeal additional conditions of a favourable opinion should be brought to the attention of the Approvals staff/REC Manager and discussed at a sub-committee of

the REC which the applicant should be invited to attend to give further representation. If the REC agrees to amend the additional conditions, the favourable opinion letter should be reissued, correspondence uploaded, and a note added to HARP. If the REC does not agree to waive the additional condition(s) of the favourable opinion which are disputed, the procedures set out in paragraph 8.15 should be followed. The applicant can either comply with the conditions or the opinion could be varied. This process may only be undertaken once for a study.

Corrective action following legally invalid opinion on a CTIMP

3.56 Annex C sets out the corrective action to be taken where evidence emerges that a CTIMP is not compliant with the Clinical Trials Regulations because the opinion given by the ethics committee is not legally valid.

Statements of compliance

3.57 Sponsors of CTIMPs are required under International Conference for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) to obtain a statement from the ethics committee issuing the ethics opinion on the trial that it is organised and operates according to GCP. All the REC standard letters issuing ethics opinions on a CTIMP include an appropriate statement of compliance with the Clinical Trials Regulations as they apply to ethics committees and the conditions and principles of GCP and should include or enclose a list of members involved in the ethics review indicating lay members and stating the profession of expert members. The statement of compliance also explains that REC quoracy is as defined in the REC Policy Document and its operating procedures are defined by the national SOPs issued by RES. No additional documentation needs to be provided to sponsors.

Publication of opinions

3.58 As per the requirements set out in the REC Policy Document, for every application reviewed by a REC a research summary, including the REC decision, is published on the HRA website no earlier than 90 calendar days after the date of the final opinion letter. Sponsors may request a deferral of publication of some fields of the research summary by emailing deferrals@hra.nhs.uk. The HRA website provides further information about the deferrals process. For Phase 1 CTIMPs involving only healthy volunteers, some fields of the research summary are automatically deferred without a need to request this. Confirmation that the deferral is in place for these trials will be provided as part of the final approval given to a trial.

Approval to proceed with research

3.59 A favourable opinion from a REC does not imply that research activity at locations can begin. Confirmation of management permission or approval from relevant care organisation(s) to proceed with the research also needs to be in place. Applicants should be informed of the requirement to work with each care organisation to obtain the appropriate management permission according to the processes in place within the UK country in which the care organisation is located. The R&D offices of NHS care organisations will not confirm that the research can proceed until all regulatory approvals are in place.

Fast-track review

3.60 A fast-track research ethics review is available for research applications that need a rapid research ethics review. This involves an advanced booking service where REC meetings can be reserved ahead of time and booked up to 7 days in advance.

3.61 Fast-track ethics review is open to global clinical trials and phase I trials for any disease type, whether the sponsor is commercial or non-commercial. This includes:

- any Clinical Trial of an Investigational Medicinal Product (CTIMP) led from UK with at least one other country participating
- any CTIMP led from outside the UK which could be placed in any country and the UK is competing for participation (including any only taking place in the UK)
- any phase I or phase I/II CTIMP in healthy volunteers or patients

The following are not eligible for fast-track ethics review:

- any CTIMP involving a gene therapy medicinal product
- any CTIMP funded by the US Department of Health and Human Services
- any other type of clinical trial or research study

3.62 For more information about the fast-track service and how to apply, see the HRA website.

Back to Contents

Section 4: Proportionate Review

Proportionate Review Service

4.1 The Proportionate Review Service (PRS) provides for proportionate review of research studies raising no material ethical issues, including projects involving straightforward issues which can be identified and managed routinely in accordance with standard research practice and existing guidelines. Proportionate Review applications are reviewed by a sub-committee rather than at a full meeting of a REC, with the final decision being notified to the applicant within 21 calendar days of receipt of a valid application. PR sub-committees may meet via videoconference or via email correspondence.

4.2 Adoption of PRS is at the discretion of the Operational Manager (or equivalent) in each part of the UK Health Departments' Research Ethics Service taking into account the nature of research reviewed by the RECs concerned and other operational considerations.

4.3 Criteria for determining whether a study is suitable for review through the PRS are developed by RES and published on the HRA website. The criteria are kept under review in the light of developments in policy and guidance, feedback from researchers and sponsors, and opinion within the Research Ethics Service.

Booking, submission and validation of applications

4.4 Bookings must be made via IRAS once the application is ready to be submitted. Studies which are identified as being suitable for PR at the booking stage will be allocated to the next available PR meeting in the UK.

4.5 The criteria for suitability for PR will be based on the 'No Material Ethical Issues Tool' (NMEIT).

4.6 Once a study has been booked to a PR meeting, the applicant must ensure that the checklist is completed correctly, and the application is submitted via IRAS with all the required supporting documentation, on the same calendar day as the booking is made. If the application is not received on the same calendar day as the booking is made, it may be withdrawn, and a new booking will need to be made via IRAS. Approvals staff/REC Managers can give an extension on the deadline at their discretion, particularly when the booking has been made several days in advance of the cut-off of the meeting.

Validation of a Proportionate Review Application

4.7 On receipt of an application assigned for proportionate review, staff should check the study's suitability for review against the current criteria as part of the validation process. Consideration should also be given to any significant ethical issues described by the applicant in the application form, which might indicate a need for review at a full meeting. Advice should be sought where necessary.

4.8 Applications submitted for PR should be validated within 5 calendar days (for validation criteria refer to paragraph 1.42). If the application is deemed to be invalid but it is reasonable that the application could be valid within the 5 calendar days, it should be marked as 'validation under consideration' on HARP. If the application does become valid then HARP should be updated to indicate when the application became valid. If the application cannot subsequently be made valid the status on HARP should be updated to 'invalid'.

4.9 As soon as the application is deemed to be invalid, HARP should be updated, and the Approvals staff/REC Manager should notify the Chief Investigator of the reasons. Where the application is invalid and also deemed to be unsuitable for PR, this should be detailed in the letter so that the application can be booked to a full REC when resubmitted.

Sub-committee procedures

4.10 A sub-committee established primarily to undertake proportionate review of new applications may consist of a mix of members, subject to the following.

- The PR sub-committee has an appointed Chair (not necessarily the Chair or vice- Chair of the REC or who may be from different RECs).
- Meetings of the sub-committee, or business conducted in correspondence, should normally be chaired by the PR sub-committee Chair. Where the PR sub-committee is not chaired by the Chair, Vice Chair or Alternate Vice-Chair of the REC, an appropriate appointment letter is required.
- The opinion on any application submitted for proportionate review will be issued by the REC of which the person undertaking chairing duties is a member ("the host REC").

Decisions on Applications

4.11 The same decisions are available to the REC for PR applications as with full applications (refer to paragraph 3.7) with the addition of:

- No opinion.

The sub-committee may decide that the application should be referred for further review at a full meeting because (a) the study falls outside the criteria for proportionate review, or (b) it raises significant ethical issues requiring wider discussion.

- There is no option to issue a request for information pending advice from a referee in Proportionate Review applications since, if the application contains material ethical issues, the application should be transferred for review at a full meeting.
- An unfavourable opinion should only be issued for proportionate review applications when the application is of such poor quality, that it would not benefit from review at a full REC meeting.

Quorum

4.12 Where a sub-committee undertakes proportionate review of a new application, the quorum is three members with at least 6 months' service on a REC, including the Chair, Vice Chair or Alternate Vice-Chair. If it is subsequently identified that a decision was issued by an inquorate PR Sub-Committee the matter should be referred to the Operational Manager. The Operational Manager will consider the application and decide whether the study should be re-reviewed at a quorate meeting.

Lead reviewers and contact with applicant

4.13 A lead reviewer must be appointed for each application to be reviewed by a proportionate review sub-committee, in consultation with the Chair as necessary.

4.14 Lead reviewers may contact the Chief Investigator (either directly or via the Approvals staff/REC Manager) prior to the review to seek any further information, clarification or assurances that may help the sub-committee to reach their decision. In doing so, they should take care not to prejudice the outcome of the review. If any amended documents are provided following a request from the lead reviewer or the sub- committee and prior to the decision being confirmed, these should be recorded in HARP and the minutes should specify that amended documents were received.

4.15 In the case of projects undertaken mainly for educational purposes, the lead reviewer may contact both the student and the academic supervisor prior to the review. Both the student and the supervisor should be notified.

No opinion and referral to full committee

4.16 Where a proportionate review sub-committee gives no opinion, the application should be referred for review at a meeting of a full REC.

4.17 The appropriate member of Approvals staff/REC Manager should contact the applicant to explain that the application is being referred to a full REC meeting.. The Approvals staff/REC Manager should identify the next suitable meeting slots available via HARP and liaise with the applicant to confirm which meeting is most suitable. The next suitable meeting slot in the UK should be offered but the applicant may refuse this and choose a more convenient meeting. The second REC should be contacted to confirm that the REC is able to accept the application. If the applicant accepts the next available meeting, the clock is not stopped during the transfer process. If the applicant refuses the first available meeting, the validation date should be reset to the closing date for submissions to the meeting concerned. Once the allocation is agreed, a letter should be sent confirming the No Opinion decision and the arrangements for further review. The reasons for referral to a full REC should be explained. All documentation connected to the application should be available to the new REC via HARP for their information.

4.18 At the full meeting, further review of the application is in accordance with the usual SOPs and all decisions are available. The 60-day clock may subsequently be stopped in the usual way if the full REC issues a request for further information in writing.

Appeal process for PR studies

4.19 Where a request is accepted to appeal an unfavourable opinion given for a study reviewed by a proportionate review sub-committee, the appeals manager will decide on the appropriate reallocation.

Back to Contents

Section 5: Suitability of research locations

General policy on multi-location studies

5.1 In the case of a clinical trial of an investigational medicinal product, the Clinical Trials Regulations provide that a single ethics opinion should be given regardless of the number of locations at which the research is to be conducted

5.2 The policy of the Department of Health and Social Care and the devolved administrations is that a single ethics opinion should apply generally to all multi-location research within the UK. The Chief Investigator should therefore submit a single application for ethics review, which should be allocated for review as specified in Section 1. The only exception to this is non-CTIMPs involving adults unable to consent for themselves and taking place at locations in both England or Wales or Northern Ireland **and** Scotland. In this case, two separate submissions are needed and two separate ethics opinions must be given under the legislation applying in each jurisdiction (see paragraph 13.37). References to NHS locations should be read to include Health and Social Care (HSC) in Northern Ireland.

Suitability of locations and investigators

5.3 An assessment of location suitability is not required for the purposes of ethics review. All Investigator locations listed in the application to the REC, and any other Investigator locations added during the course of the study, are deemed to have ethics approval as part of the original favourable opinion from the REC. Research should not be conducted by any organisation, or on participants under the duty of care of that organisation, until the relevant management permission/confirmation of capacity and capability (as appropriate to the type and location of the organisation) is given for that organisation.

6.1 For CTIMPs, clinical investigations of medical devices, and combined CTIMPs and clinical investigations of medical devices, the sponsor needs to include in their application what arrangement they have in place to ensure they select suitable locations and investigators. A change of investigator at a location, in a multi-centre trial, or the additional of a new location which requires investigator oversight, is a modification of an important detail (see section 6 for more information on this modification type). There will be no different expectations depending on whether the trial is taking place in the NHS or not. If there is a change to the way in which a location or investigator is selected, then this would be a substantial modification.

The Principal Investigator

5.4 The Principal Investigator (PI) is the individual responsible for the conduct of a research study at an Investigator Location. One Investigator Location may comprise of one or more trial locations. The 'Set up of research activity at NHS organisations' guidance in IRAS includes a definition of Investigator Location, trial location and information on the appropriate level of PI oversight. The principal scope of this guidance is interventional heath care research in the NHS however, the principles can also be applied to interventional research at non-NHS locations and non-interventional research, generally.

5.5 A "single location study" is a study that the Chief Investigator plans to conduct at one Investigator Location only in the United Kingdom. In a non-CTIMP, the Chief Investigator (CI) should also be the Principal Investigator (PI) for the location. In the case of a single-location CTIMP, the CI and PI must be the same person.

5.6 A "multi-location study" is a study that the Chief Investigator proposes should have more than one Principal Investigator, that is to say that the study should be conducted at more than one Investigator location in the UK. The Chief Investigator may also be the Principal Investigator for one of the Investigator locations. It is the responsibility of the Chief Investigator to ensure that a suitably qualified professional is appointed as the Principal Investigator for each Investigator location. In a CTIMP, the Principal Investigator and all other named investigators must be "healthcare professionals" (see definition in the Glossary).

5.7 Principal Investigators are responsible to the Chief Investigator for complying with the terms of the REC application and the protocol.

Trial locations and Investigator locations

5.8 The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 provide the following definitions, specifically for Clinical Trials of Investigational Medicinal Products (CTIMPs): 'trial location' means 'a hospital, health centre, surgery or other establishment or facility at or from which a clinical trial, or any part of such a trial, is conducted;'

5.9 'investigator' means, in relation to a clinical trial, the healthcare professional responsible for the conduct of that trial at a trial location, and if the trial is conducted by a team of healthcare professionals at a trial location, the investigator is the leader responsible for that team;'

5.10 Whilst ICH-GCP (E6(R3)) provides the following definitions, specifically for CTIMPs:

a) **Investigator:** A person responsible for the conduct of the clinical trial, including the trial participants for whom that person has responsibility during the conduct of the trial. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal investigator. Where an investigator/institution is referenced in this guideline, it describes expectations that may be applicable to the investigator and/or the institution in some regions. Where required by the applicable regulatory requirements, the "investigator" should be read as "investigator and/or the institution."

b) I**nvestigator Location:** The location(s) where trial-related activities are conducted and/or coordinated under the investigator's/institution's oversight.

5.11 An Investigator Location is defined by the PI's ability to effectively oversee the research activities taking place there. It is not determined by whether the locations are within the same legal entity, are under the same management, or whether the individuals undertaking those activities share the same employer. Further information is included in the 'Set up of research activities at NHS organisations' guidance in IRAS.

5.12 In the case of research conducted within the NHS, each trial location will in most cases be one of the following: An NHS Trust (in England).

- An NHS Trust and Local Health Board (in Wales).
- An NHS Health Board (in Scotland).
- A Health and Social Care Trust (in Northern Ireland).
- A GP practice or NHS dental practice.

Guidance on specific scenarios is available in IRAS.

5.13 To effectively oversee research activity, any one legal entity might have one, or more than one, Principal Investigator, and/or there may be one Principal Investigator for more than one legal entity. Appropriate Principal Investigator oversight in interventional research is described in the Set-up of research activity at NHS organisations' guidance in IRAS. Similar principles apply in non-interventional research (that the research activities within one Investigator Location is determined by whether those activities may be most effectively overseen by one Principal Investigator). For example, a large geographical area could be identified as the Investigator location for some studies in public health, epidemiology or needs assessment.

5.14 The same principles included in the Set-up of research activity at NHS organisations (interventional research) IRAS guidance also apply to non-NHS locations.

5.15 Trial locations outside the NHS could include the following:

a) an academic institution;

b) a research centre funded by the voluntary sector;

c) a Government Department or other public body;

d) a Prison Service establishment, local authority secure unit or Home Office secure training centre;

e) a private company or corporation (for example, a pharmaceutical or biotechnology company or clinical research organisation);

f) a private hospital or private clinical practice;

g) an employee-led social enterprise.

5.16 Where the research location is outside the NHS in terms of accountability (is not part of an NHS investigator location), but is using NHS facilities by agreement (for example, a private practice based at a GP surgery or a private research unit renting premises at a NHS hospital), the name of the organisation responsible for the research conduct should be clearly distinguished from the NHS organisation concerned (and it should be clear to potential and actual research participants that the NHS is not involved and that they are not under NHS care for the purposes of the research).

5.17 In some cases, an NHS Investigator location may include activities undertaken by or at non-NHS organisations. For example, MRI scans may be undertaken on premises owned by universities, research charities or private companies. These activities are still within the one NHS Investigator Location, as long as the NHS Principal Investigator is responsible for overseeing them. If separate PI oversight arrangements are needed, the activities are within a separate Investigator Location.

5.18 Trial locations are organisations responsible for participant-related research procedures specified in the protocol and overseen by a Principal Investigator, including recruitment and informed consent (there may be one or more trial location overseen by one principal investigator, or one trial location may have one or more principal investigator).

5.19 The following are not considered to be trial locations as they do not undertake activities requiring PI oversight:

a) Participant Identification Centres (PICs), i.e. organisations from which clinicians or clinical units refer potential participants to the research team based in another organisation, for assessment and possible recruitment to a study.

b) Data Collection Centres (DCCs) or Tissue Collection Centres (TCCs) in the context of applications for ethics review of research databases or research tissue banks respectively (see paragraph 11.29and 12.25).

c) Research units undertaking support functions, e.g. project management, location monitoring, data analysis or report writing.

Responsibility for assessing the suitability of locations and investigators

Location Assessment at NHS and non-NHS locations

5.20 The REC does not undertake location specific assessments. A standard condition of a favourable opinion from the REC is that Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) at the organisation level should be obtained prior to any research project activity commencing at an Investigator location within the NHS or Health and Social Care in Northern Ireland (HSC).

5.21 For non-NHS locations, it is expected that sponsors have arrangements in place to ensure selection of suitable locations and investigators. For CTIMPs, investigations of medical devices, and combined CTIMP and medical device studies, these arrangements need to be submitted to the REC for review with the initial application, and significant changes to these arrangements treated as a substantial modification. This replaces the previous requirements for the REC to conduct an assessment of the non-NHS location.

Accreditation of Phase 1 trial units by the MHRA

5.22 The MHRA GCP Inspectorate operates a voluntary scheme of accreditation for commercial trial units undertaking Phase 1 trials in healthy volunteers. Details of the scheme and a list of accredited units are published on the MHRA website.

5.23 The location assessment for Phase 1 trial locations should take the accreditation status of the location into account. It is not necessary for the REC to review issues routinely addressed by the GCP inspectors as part of the process leading to accreditation. The inspectors will notify the HRA when a unit has been accredited

and will provide a copy of the application form submitted by the unit, the inspection report and closing statement, and the accreditation certificate. This information will be made available centrally to all Phase 1 RECs. Any critical findings identified during inspection will be promptly notified to RES so that these can be considered in any reviews undertaken prior to the issues being resolved and accreditation confirmed.

5.24 Reassurance as to the suitability of the location may be gained from the registration of the location within the MHRA Phase 1 Accreditation Scheme.

Review of general advertising and screening procedures at clinical trial units

5.25 Clinical trial units, particularly Phase 1 units, may undertake general advertising and screening procedures to recruit potential trial participants to a pool of volunteers, prior to inviting such volunteers to participate in a specific trial. This activity constitutes preparations for undertaking a trial and is not part of the conduct of a trial under the Clinical Trials Regulations. It is therefore not a legal requirement for the procedures to be reviewed by an ethics committee and a favourable opinion obtained. However, Phase 1 trial units should seek ethics advice on these generic procedures. Requests for advice should be submitted in writing to GDRC@hra.nhs.uk enclosing relevant documentation such as advertising material or screening protocols. The request should not form part of the main application relating to a particular trial.

Addition of new locations and Principal Investigators

5.26 Procedures for extension of a study to new Investigator locations, appointment of new Principal Investigators or other location-specific modifications are set out in paragraphs 6.60 – 6.68.

Closure of locations

5.27 There is no requirement for the Chief Investigator or sponsor to notify the REC where an approved location is closed or withdrawn from the study prematurely for example, if the Principal Investigator withdraws from the study or the sponsor decides that the location is no longer suitable. There is no requirement for the Chief Investigator or sponsor to notify the REC of the routine closure of active locations at the conclusion of a study. The Chief Investigator or sponsor must declare the end of a study to the REC, and MHRA as appropriate, using the appropriate end of study form.

5.28 A substantial modification is required only for a temporary halt at a study location, if

this temporary halt is to protect participants from harm (see paragraph 6.23). The REC may request further information regarding the reasons for the closure of the locations if it has any concerns (for example, if there are concerns regarding the welfare of participants who had already been recruited).

Monitoring of research locations

5.29 Operational policy on the monitoring of research is set out in Section 10. In general, the REC is not responsible for proactive monitoring of research. However, it has a duty to keep the favourable ethics opinion under review in the light of any significant developments and may review the opinion at any time.

5.30 The REC is not responsible for proactive monitoring of the conduct of the research at individual locations. However, where information comes to the attention of the REC that raises questions about the suitability of the location or investigator, the favourable opinion for the location may be reviewed. Procedures for review of opinions and for suspension or termination of opinions in non-CTIMPs are set out in paragraphs 10.72 – 10.92. Only the REC has authority to suspend or terminate an opinion, whether for the study as a whole or an individual location.

5.31 The REC may request additional information for a particular location at any time in the light of concerns brought to its attention from any source. It may do so by writing to the Chief Investigator and sponsor.

Modifications to multi-location research

5.32 Procedures for reviewing modifications to multi-location research are set out in Section 6, including extension to additional Investigator locations), appointment of new Principal Investigators and location-specific protocol modifications (paragraphs 6.60 – 6.68.).

Back to Contents

Section 6: Modifications to research given a favourable opinion

Statutory requirements

6.1 Modifications refer to any change made to a study following the outcome of a Favourable Opinion. Modifications can be categorised as “substantial” (requiring REC review), a “modification of an important detail” (which the MHRA and REC only need to be made aware of for administrative purposes) or a “minor modification”, which can be implemented without informing the MHRA or REC (note the term “minor modification” is not a definition used in the Regulations, it refers to modifications that are neither classed as substantial nor modifications of an important detail). See Annex B for examples of these types of modifications.

6.2 Where the modification is substantial, the sponsor is required to submit a valid modification to the MHRA and/or the REC that gave the favourable opinion of the trial. Where there is more than one sponsor for the research, “the sponsor” refers to the sponsor that has been designated to take responsibility for all matters relating to modifications.

A “modification to a clinical trial authorisation” is defined broadly in the Clinical Trials Regulations as a modification to any of the following:

(a) the terms of the request for clinical trial authorisation from the MHRA;

(b) the terms of the REC application;

(c) the protocol;

(d) any other particulars or documents submitted with the applications to the MHRA or the REC.

A “substantial modification” is defined as a modification that is likely to affect to a significant degree any of the following:

(e) the safety or physical or mental integrity of the participants of the trial,

(f) the scientific value of the trial,

(g) the conduct or management of the trial, or

(h) the quality or safety of any investigational medicinal product used in the trial.

6.3 For substantial modifications (where a REC review is required), the modification should be confirmed as valid within 7 calendar days of being submitted. Where there

are issues that prevent a modification from being valid, these will be raised with the applicant and if they cannot be addressed within 7 calendar days the modification will be invalid, and the sponsor would need to submit a new modification. Following confirmation of a valid modification, the REC will conduct an initial review and issue an outcome within 35 calendar days. RECs can issue a favourable opinion, a favourable opinion with additional conditions, an unfavourable opinion (non-CTIMPs only) or a request for further information. For CTIMPs, an unfavourable opinion cannot be issued at initial review, instead, where the REC is not able to issue a favourable opinion, they will request further information in the first instance. Where further information is requested, the sponsor will have 60 calendar days to respond to this request. If required, the sponsor can request an extension from the REC. Once their response is received, the REC have an additional 10 calendar days to provide a final opinion – a favourable opinion, favourable opinion with additional conditions, or an unfavourable opinion.

6.4 Modifications to clinical investigations being carried out under the provisions of the Medical Devices Regulations must be notified in all cases to MHRA (Devices).

General policy

6.5 The policy of the UK Health Departments is that the statutory provisions relating to substantial modifications to CTIMPs should generally apply to the review of substantial modifications to any research study that has previously received a favourable ethics opinion from a REC. There will however be some procedural differences, which are indicated in this section. The 35 day clock applies to review of all substantial modifications, except those proposing to include adults lacking capacity for the first time in a non-CTIMP, where 60 calendar days is allowed for the review and the clock may be stopped once to request further information or clarification (see 13.39 – 13.43).

6.6 Substantial modifications may be reviewed by a sub-committee of the REC, or where time allows, at a meeting of the Committee. They should not be reviewed by the Chair acting alone.

Procedures for notifying modifications

Notification before the commencement of the research

6.7 A study is generally considered to have commenced when any of the procedures set out in the protocol are initiated. Occasionally the sponsor or Chief Investigator may propose to revise the terms of the REC application, the protocol or other supporting

documentation after a favourable opinion has been given but before the study commences. If this revision meets the criteria for a substantial modification, it should be notified and reviewed in the same way as would happen for a substantial modification submitted after the study has started.

6.8 A substantial modification may exceptionally be submitted with or during the initial application for ethics review. For example it could be necessary in an international study where the trial has already started, and significant issues have arisen in the conduct of the trial, or where issues are raised in the course of regulatory applications in other countries. The sponsor might then need to amend the protocol and notify this as a substantial modification to regulatory authorities and ethics committees in each country. In these circumstances it is acceptable for a substantial modification to be included as part of the initial application package or submitted during the review process. If the REC's opinion is favourable, the modification may be listed with the documents approved in the favourable opinion letter for the study. There is no need to issue a separate opinion letter for the modification. However, if the modification is submitted during the ethics review and there is insufficient time to review it within the 60-day period, it may be reviewed separately and an opinion given following the issue of the opinion on the main application and within 35 calendar days of receiving the modification.

Notices of modification

6.9 For CTIMPs, the substantial modification may be submitted by any one of the sponsor, the sponsor's legal representative, or another person or organisation authorised by the sponsor.

6.10 For all other research, the substantial modification may be submitted by either the sponsor or Chief Investigator.

6.11 In all cases, the substantial modification should summarise the change(s) included in the modification and briefly explain the reasons in each case or refer to supporting documentation explaining the changes. One modification may refer to a number of different changes. The description of the modification should be completed in language comprehensible to a lay person and submitted with any relevant supporting documentation, including the study protocol, which are clearly marked with the changes being made. If the changes listed are unclear, the modification may be marked as invalid and further information requested.

6.12 How modifications are submitted depends on the type of research:

(a) For Research Tissue banks and Research Databases, a 'Notice of Substantial

Amendment Form' should be completed and submitted via the online modification submission alongside any supporting documentation.
(b) For CTIMPs submitted via combined review, the modification tool should be completed and submitted, alongside any supporting documentation, via the new part of IRAS.
(c) For other studies, the modification tool should be completed and submitted, alongside any supporting documentation, via the online modification submission.
In all cases, any documents that have been modified should show both the previous and the new wording. It is acceptable for extracts to be provided or for the changes to be listed in a separate document, showing both the previous and the new wording.

6.13 The sponsor or Chief Investigator may also include other supporting information, such as a summary of trial data, an updated safety analysis or a report from a trial monitoring committee. Where the modification could significantly affect the scientific value of the research, it may be helpful if further evidence of scientific review commensurate with the scale of the research is provided.

Validation of modifications

6.14 The period of 35 calendar days, within which an ethics opinion must be given, normally begins when a modification is confirmed as valid. The clock will be stopped where a request for information is issued.

6.15 The relevant date ("the validation date") is the working day on which the modification is confirmed as valid.

6.16 A substantial modification should be accepted as valid if all the following criteria are met (for CTIMPs submitted via the combined review service, the MHRA conducts the formal validation process for modifications, but a light touch validation should be carried out to ensure criteria are met):

(a) The modification has been completed in full, including the sponsor's modification number.

(b) Relevant extracts or new versions of revised documents have been submitted, showing the new version number and date and giving both the previous and new wording which is clearly identifiable.

(c) The modification has been electronically authorised by the sponsor or authorised delegate. For Research Tissue Bank applications, the modification should be electronically authorised by the applicant. For Research Database applications, the modification should be electronically authorised by the Data

Controller.

(d) The study is still in progress, i.e. the end of the study has not yet been declared.

(e) In non CTIMPs, where the modification proposes to include adults lacking capacity in the research for the first time, the additional documents listed in paragraph 13.39 should be submitted. This type of modification should be reviewed by a full REC rather than by a sub-committee.

(f) Where the modification proposes to change (including an increase or decrease) the exposure of participants to ionising radiation, or to include such exposure for the first time, Part B Section 3 of the application form in IRAS should be updated or completed (as appropriate). This should be submitted to the REC by a further electronic submission of the form.

(g) Where the modification proposes to include existing or newly obtained tissue samples for the first time, Part B Section 5 of the application form in IRAS should be completed. This should be submitted to the REC by a further electronic submission of the form.

6.17 It is the responsibility of the Approvals Administrator/REC Manager to decide whether or not the modification is valid and to notify the sponsor and Chief Investigator using the relevant standard letter (valid notice or invalid notice). Validation is confirmed by the MHRA for modifications submitted via the CTIMP combined review service. Notification will be given within 7 calendar days of receipt, except that there is no need to issue a validation letter if the sub-committee is able to review the modification and reach an opinion within 7 calendar days.

6.18 Where there are any issues preventing the modification being valid, these should be raised with the applicant as soon as possible so that validation can be confirmed within 7 calendar days (this does not apply for modifications submitted via the CTIMP combined review service). Whilst issues are being addressed, the substantial modification should be marked as ‘validation under consideration’ on HARP. If the substantial modification cannot be made valid within 7 calendar days of submission, or prior to the cut-off date for the REC meeting (whichever is sooner), it should be changed from ‘validation under consideration’ to ‘invalid’ on HARP and withdrawn from the meeting.

Deciding whether a modification is substantial

6.19 For all studies, it is the responsibility of the sponsor to determine whether a modification is substantial. Equally, if the sponsor is satisfied that a modification is not substantial, there is no requirement to notify the REC unless it is a modification of an important detail (see paragraph 6.29).

6.20 Sponsors and CIs may seek advice on whether a modification should be considered substantial. When giving advice, it should always be made clear that it is ultimately the sponsor's responsibility to determine whether a modification is substantial. Sponsors should complete the modification tool, which should provide guidance on whether the modification is substantial or not, and what reviews or approvals are required.

6.21 In giving advice, consideration needs to be given to whether the proposed changes will affect the research "to a significant degree". Particular account should be taken of any implications for the safety or welfare of participants, and of any information that participants might require to give informed consent to continue to participate in the research as amended.

6.22 It is recommended that where there is any doubt about the potential implications of the modification for participants, it should be treated as a substantial modification and reviewed by the REC.

6.23 The following changes should normally be regarded as substantial (see Annex B for examples of CTIMP modifications and where MHRA authorisation would be required):

- Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value.
- Changes to the procedures undertaken by participants.
- Changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study.
- Significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers.
- Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a CI (see 6.74 - 6.76)

- A change to the insurance or indemnity arrangements for the study.
- A change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.
- Temporary halt of a study or temporary halt at a study location to protect participants from harm, and the planned restart of a study following a temporary halt (see paragraph 10.58 –10.79).
- A change to the definition of the end of the study (see paragraph 10.63).
- Any other significant change to the protocol or the terms of the REC application.

This list of examples relates to substantial modifications for REC purposes. Applicants undertaking research in the NHS/HSC should also refer to IRAS help.

6.24 There will, however, be changes to the details of research that have no significant implications for participants or for the conduct, management or scientific value of the study and are modifications that are not substantial. These types of modification can fall into two categories: (1) modifications of important details (where the REC should be notified for information) and (2) minor modifications (where the REC does not need to be notified).

Examples of modifications of important details are as follows (for CTIMPs, there are further examples in Annex B):

- Change of sponsor (it is not a legal requirement for the REC to consider the suitability of the sponsor so this would not be a substantial modification unless the change in sponsor would require changes to insurance arrangements or study documents beyond just changing the sponsor name).
- Increase in duration of the study, provided that the exposure to treatments is not extended, the definition of the end of study is unchanged and there is no change to monitoring arrangements or procedures to participants.
- For CTIMPs, changes of investigator (other than CI)
- Changes to contact details for named contacts on the study, for example the sponsor or CI

- Changes to the Chief Investigator's research team.
- For CTIMPs, addition of any new locations (NHS/HSC or non-NHS/HSC)
- For CTIMPs, the date of recruitment of first participant

This list of examples relates to modifications of important details for REC purposes. Applicants undertaking research in the NHS/HSC should also refer to IRAS help.

6.25 If a modification is not substantial nor a modification of an important detail, then these can be regarded as minor modifications. Sponsors do not have to inform the REC of these changes. Examples might be as follows:

- Changes in the documentation used by the research team for recording study data.
- Changes in the logistical arrangements for storing or transporting samples within the duration of the project.
- Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications.

The list of examples relates to minor modifications for REC purposes. Applicants undertaking research in the NHS/HSC should also refer to IRAS help.

Substantial modifications to CTIMPs – authorisation or ethics opinion?

6.26 It is the responsibility of the sponsor to decide whether a substantial modification requires authorisation, or an ethics opinion, or both. There are examples in Annex B.

Substantial modifications to CTIMPs notified for information only

6.27 Where a substantial modification to a CTIMP requires authorisation by the MHRA only, there is no requirement to notify the REC. Where it is notified voluntarily, receipt should be acknowledged within 30 calendar days to the sponsor (or other person submitting the notice on behalf of the sponsor).

6.28 The modification should be seen and noted by the Chair. There is normally no requirement to notify the Committee. However, if the Chair considers exceptionally that the modification could affect the ethics opinion as well as the clinical trial authorisation, the matter may be discussed at a meeting of the sub-committee or Committee. A letter may be sent to the sponsor advising that, in the view of the REC, an ethics opinion should have been requested and making any comment on ethical

issues raised by the modification. Although in the case of a CTIMP it is primarily for the sponsor to interpret the guidance on the need for ethics review of modifications, the REC may review any information it receives in consultation with the MHRA (see Section 14).

Notification of minor modifications and modifications of important details

6.29 Where changes are made to a research study that the sponsor does not consider to be substantial modifications, there is no requirement to obtain an ethics opinion. These modifications can fall into one of the following two categories:

(a) modifications of important details: these modifications do not significantly impact participant safety or rights, which the REC only needs to be made aware of for administrative or oversight purposes. These types of modification are not reviewed by the REC and no opinion will be issued, they are for information only. They may however need other approvals such as HRA and HCRW Approval. See paragraph 6.24 for examples.

(b) minor modifications: these modifications do not need to be notified to the REC for information. They can be implemented at any time without informing the REC, although other approvals such as HRA and HCRW Approval may be required. See paragraph 6.25 for examples.

6.30 Where a sponsor or Chief Investigator notifies the REC of a minor modification, but it is considered that it should have been regarded as substantial and requires ethics review, the matter should be brought to the attention of the Chair and, if the Chair agrees, may be discussed at a meeting of the sub-committee or Committee. In the case of a CTIMP it is for the sponsor to interpret the guidance on what is substantial. However, the REC may review any information it receives.

6.31 Where the study has been marked as finished, modifications are not accepted. However, it can be helpful to the REC to be made aware of changes affecting key individuals which occur during the follow up to the completion of a study. For example, CI, PI, trial manager or sponsor contacts may change.

Review of substantial modifications

6.32 Substantial modifications should be reviewed by a sub-committee of the REC (see Section 7) or by the Committee itself, e.g. where Adults Lacking Capacity are being included for the first time. They may not be reviewed by the Chair acting alone.

6.33 The Chief Investigator and/or a representative of the sponsor may be invited to attend

a sub-committee or Committee meeting to respond to questions about the modification.

6.34 The decision reached should be a favourable opinion, favourable opinion with additional conditions, request for further information, or unfavourable opinion (non-CTIMPs only). For CTIMPs, an unfavourable opinion cannot be issued at initial review, instead, where the REC is not able to issue a favourable decision, it will request further information in the first instance. (see paragraph 6.38).

6.35 It is not permitted to give a favourable opinion for part of the substantial modification only. The sponsor and Chief Investigator should be notified of one of the following decisions:

- Favourable opinion
- Favourable opinion with additional conditions
- Request for further information
- Unfavourable opinion (for CTIMPs, this can only be issued following a request for further information in the first instance)

The opinion letter should include the same information that would be included in an opinion letter on a new application (see paragraph 3.11), including a contact point for receipt of queries from the applicant.

6.36 Where a REC has given a final opinion, either favourable, favourable with additional conditions or unfavourable, and subsequently receives information suggesting that the opinion is based on a factual error or misunderstanding, it may vary its opinion (see paragraphs 3.51 - 3.55).

6.37 Where an unfavourable opinion on the modification may be given on safety grounds, the Approvals staff/REC Manager/Chair should correspond with the MHRA prior to the decision being taken. The MHRA is notified automatically of all opinions on substantial modifications through its access to HARP. Where the MHRA has been asked to approve a substantial modification, it will issue the outcome within 35 calendar days. It is the responsibility of the sponsor to arrange for the REC to be provided with a copy of the notice for information.

Requests for further information

6.38 The REC (and for CTIMPs, the MHRA) can request further information when reviewing substantial modifications. The REC will only request further information where it identifies issues that otherwise prevent the substantial modification from

receiving a favourable opinion or favourable opinion with additional conditions. Requests for further information for substantial modifications will only be issued in a minority of cases.

6.39 The request for further information will be sent within 35 calendar days of the substantial modification being confirmed as valid. The sponsor has 60 calendar days to respond unless an extension to this timeframe has been agreed. Where an extension is required, the sponsor can request this from the REC (or for CTIMPs if the request is only relevant to MHRA, then the sponsor should request this from the MHRA directly). The request should outline why an extension is needed and when they can expect to respond.

6.40 Where the sponsor does not respond to the request for further information within 60 calendar days (or within an agreed extended timeframe), the modification will receive an unfavourable opinion.

6.41 Once the sponsor submits a response to a request for further information, the REC (or for CTIMPs, the REC and/or MHRA) will decide on the outcome within 10 calendar days.

6.42 There are three possible outcomes from the REC after they review a response to a request for further information:

- Favourable opinion
- Favourable opinion with additional conditions
- Unfavourable opinion

Following a request for further information, if a substantial modification is given an unfavourable opinion, the sponsor can appeal this within 28 calendar days of receiving the outcome (see paragraph 6.43). In their email, the sponsor would also need to outline why they disagree with the outcome issued for the modification.

Appeals

6.43 There is no statutory provision for appeal against a decision of the REC to give an unfavourable opinion of a substantial modification. However, an applicant may request leave to appeal by writing to the relevant Appeal Manager for the REC concerned (see paragraph 8.16) within 28 calendar days of the date of the opinion letter, setting out representations with respect to the opinion. Leave to appeal will normally be granted, although the Appeal Manager has the discretion to refuse leave

where there are no reasonable grounds for appeal. The Chair of the REC should be notified of the receipt of the appeal.

6.44 Where an appeal is granted, the Appeal Manager should arrange for the modification documentation, including the opinion letter and the applicant's representations, to be sent to another REC ("second REC") for its comments. The documentation should be reviewed by the Chair and at least one other member of the second REC and comments provided in writing to the original REC, copied to the Appeal Manager, within 14 calendar days of receipt by the appeal REC.

6.45 Alternatively, the Appeal Manager can arrange for the modification documentation to be sent to an appropriate specialist advisor. Comments should be provided to the Appeal Manager, who will forward to the original REC, within 14 calendar days of the request being sent to the advisor.

6.46 Where it could be helpful to the appeal REC in reviewing the appeal, the Appeal Manager may also seek advice from other referees; draw the attention of the appeal REC to published guidance or arrange for further guidance to be provided on issues of law, regulation or operational procedure.

6.47 Once all external comments and additional guidance have been provided, the Approvals staff/REC Manager of the original REC should submit the modification documentation, together with the applicant's representations, for re-review at the next sub-committee or full meeting of the original REC. The sponsor's representative or Chief Investigator may be contacted or invited to attend the meeting to answer questions.

6.48 The REC should reach one of the following decisions at the meeting:

- Favourable opinion
- Favourable opinion with additional conditions
- Unfavourable opinion (for CTIMPs, this would only be issued following a request for further information).

The REC may indicate support for some parts of the modification when issuing the unfavourable opinion.

The decision should be communicated to the applicant in writing within 7 calendar days of the meeting.

6.49 The original REC remains fully responsible for the opinion and may confirm its original unfavourable opinion if it continues to believe that the modification is ethically

unacceptable. Where it does so, it should demonstrate in the letter to the applicant that it has given due consideration to the representations and reasons for rejecting them.

Variation of Opinion

6.50 A request may be made to vary the opinion where it appears to be based on error or misunderstanding (see paragraphs 3.51– 3.55).

Modifications requiring submission of a new application

6.51 RECs must always adopt a **proportionate** approach in assessing whether a modification may be reviewed as submitted or whether a new application should be requested. A new application should only be required where a proposed modification would **fundamentally** alter the nature of the research and the extent of the involvement of, or risk to, existing and/or potential participants. Examples might be where the proposed modification involves:

- A change in the primary purpose or objective of the research, such as introduction of additional genetic studies;
- A substantial change in research methodology;
- Introduction of new and substantially different classes of investigations or other interventions (rather than simply re-scheduling or modifying those already approved);
- Recruitment of a new category of participant (especially if these would be regarded as being from vulnerable groups);
- A proposed sub-study with a different Chief Investigator
- Where a modification involves the submission of a separate protocol.

6.52 Where a REC requests submission of a new application, it should give reasons to the applicant with reference to the above criteria. Where substantial modifications relate to a CTIMP, the decision whether a new application should be submitted is primarily the responsibility of the MHRA. The MHRA's decision should therefore be taken into consideration; this is regardless of whether the CTIMP was approved under the combined review service or the standard review service. If the MHRA decision is unknown, the REC is encouraged to liaise with the MHRA via ctdhelpline@mhra.gov.uk.

6.53 By virtue of their design, studies which have been set up as Complex Innovative

Trials (sometimes referred to as adaptive, platform or umbrella trials) may add different interventions or may recruit new categories of participants as the study progresses. For Complex Innovative Trials, it is acceptable for these changes to be submitted as a substantial modification rather than as a new application. However, for trials to come under the heading of a Complex Innovative Trial, the protocol must have been approved by the REC on this basis when the study was originally reviewed and the methodology included in the protocol should have been clear about the scope for future phases, treatment arms or other adaptive features. Where the changes included in the modification are particularly significant (this applies beyond CTIMPs which fall under the category of Complex Innovative Design Trials), the modification may be reviewed by a sub-committee involving a larger number of members or by reviewing the modification at a full REC meeting.

6.54 A common approach must always be adopted in CTIMPs between the REC and the MHRA. Where the MHRA accept that a change can be made via a modification, the REC should process the modification. There will continue to be situations where it may be relatively straightforward to process a modification at the MHRA, but which will have significant implications for the REC. Where the REC has concerns, it is important to have an early dialogue with the MHRA to discuss the issues. Details of any discussions with the MHRA should be uploaded to HARP.

6.55 Where a complex or extensive modification is to be considered by the REC, it may be more appropriate to establish a sub-committee of more than the usual number of members if that would be helpful or to allocate the modification to a slot at a meeting of the full committee. In either case, the researcher may be invited to attend. Either option may compromise timelines and, if this does happen, the reasons should be noted and recorded on HARP.

6.56 All applications reviewed under PRS (Proportionate Review Service) should match the ‘No Material Ethical Issues Tool’ (NMEIT). Any subsequent proposed substantial modifications to such studies may be reviewed by the PRS Committee or any other sub-committee (SC). Where the proposed changes are significant, the SC may consider that:

a) the modifications are reasonable but raise significant or complex ethics issues which the sub-committee considers need wider discussion – it should refer the modification to a full meeting of the REC; or

b) the modifications are unreasonable because they should be subject of a new application according to the guidance in SOPs.

It does not necessarily follow, where modifications to a PR application would make the application fall outside the NMEIT, that a new application is required. The relevant guidance listed above should be applied.

6.57 If a modification to a study which did not previously require a REC review is submitted to the lead coordinating function, and the nature of the changes means that the project would now require a REC review under the REC Policy Document (e.g. a study which previously only involved NHS staff was expanded to also recruit patients), the sponsor should be directed to seek advice from an Operational Manager in the lead nation for the study.

Modifications to multi-location studies

6.58 The Chief Investigator should notify local Principal Investigators and research collaborators that they should inform the R&D office for the care organisation, in case the modification has implications for research governance approval of the research.

6.59 Where the REC considers it reasonable to give a favourable opinion on the modification without a new application, but remains concerned about possible ethical implications at individual locations, it should proceed as follows:

- A favourable opinion with additional conditions should be issued within 35 calendar days.
- The conditions should relate to implementation at locations. For example, the opinion might be given on the condition that the modification will not be implemented at any location lacking the appropriate facilities, or that any additional support required by participants will be provided locally. The sponsor or Chief Investigator could also be required to send a copy of the opinion letter to the care organisation responsible for research governance at the location. The responsibility would then lie with the sponsor and the care organisation to ensure that it was reasonable for the modification to be implemented.
- In the light of any location-specific concerns, the REC may review the favourable opinion for a non-NHS location at any time (see paragraphs 10.72 — 10.92).

Modifications relating to individual locations

6.60 The sponsor may extend the study to additional NHS/HSC and non-NHS/HSC locations, subject to obtaining permission from the NHS/HSC care organisation or other organisation responsible for participants at the location. The location(s) are

deemed to be approved within the terms of the favourable opinion for the study from the REC.

6.61 There is no requirement to submit a substantial modification to the REC, either for NHS/HSC or non-NHS/HSC locations. The addition of a new location should be categorised as a modification of an important detail provided that the way in which the sponsor selects the location is not changing. If there is a change to the way in which a location is selected, then this would be a substantial modification.

Appointment of a new Principal Investigator at a location

6.62 In a CTIMP, the appointment of a new Principal Investigator is classified as a modification of an important detail. The addition of a new investigator should be categorised as a modification of an important detail provided that the way in which the sponsor selects the investigator is not changing. If there is a change to the way in which an investigator is selected, then this would be a substantial modification.

6.63 Where possible, arrangements to notify the modification and permission from the host organisation should be made in advance by the sponsor so there is no interruption to the approvals in place. Where an interruption is unavoidable, for example due to an unforeseen absence, the sponsor should arrange for a suitable individual to act as interim PI and seek the necessary approvals as soon as possible. The trial may continue at the location pending confirmation of approval for the new PI. Protocol procedures may continue provided that the sponsor is satisfied that suitable interim arrangements are in place for supervising the study.

6.64 Other changes to the local research team at individual locations would be classified as minor modifications.

6.65 For all other studies, there is no requirement to notify the REC of the appointment of a new Principal Investigator or Local Collaborator. At NHS/HSC locations, the R&D office should be notified of the appointment and continued permission sought.

Location-specific modifications to the protocol or participant information

6.66 In multi-location studies it may be necessary for location-specific modifications to be made to the research procedures in the protocol or to study documentation such as the participant information sheet. Where such modifications meet the criteria for minor modifications (see paragraph 6.24), the sponsor may authorise the modification without notifying the REC or seeking an ethics opinion. For example, the generic participant information sheet will normally be customised to give local contact numbers and information about complaints procedures and, where

applicable, independent advisers.

6.67 Where a location-specific modification is substantial, a substantial modification should be submitted to the REC for review according to normal procedure. Guidance on the consideration of location-specific issues is given in paragraph 6.66.

6.68 Where significant local variations in protocol procedures or information for participants can be expected at the outset, the sponsor and Chief Investigator should reflect these as far as possible in the REC application. For example, the protocol may allow a choice of comparator regimes or variation in standard radiation dose, depending on normal clinical practice at each location. Where appropriate, the generic participant information sheet may include text options to be selected by the local Principal Investigator, depending on local practice. The REC should then consider whether such variation is permitted within the terms of the single ethics opinion for the study.

Appointment of a new Chief Investigator or Sponsor

6.69 The appointment of a new Chief Investigator is a substantial modification, requiring a favourable opinion from the REC. In addition to the modification (which should be signed by the sponsor or authorised delegate), the applicant should submit:

- A copy of the new Chief Investigator's CV.
- The IRAS application form, signed by the new Chief Investigator (not applicable to CTIMPs submitted via combined review).

6.70 If the new Chief Investigator will also be appointed as a new local Principal Investigator at a research location, this should be made clear on the modification documents. If it is an NHS location, the R&D office should be notified.

6.71 The appointment of a new sponsor is a modification of an important detail. In addition to the modification (which should be signed by the outgoing sponsor) the applicant should submit the IRAS application form signed by the new sponsor (note, this is not applicable to CTIMPs submitted via combined review).

Absence of Chief or Principal Investigator

6.72 From time to time, Chief Investigators or local Principal Investigators may be absent due to annual leave, sick leave, maternity leave, sabbatical or for other reasons. For short absences, the CI or PI is responsible for arranging adequate cover. Where this has not been possible, for example because the absence was unforeseen, the research sponsor will be responsible for ensuring that appropriate arrangements are

made for the continued conduct of the study. The care organisation hosting the research is normally responsible for monitoring the conduct of the study.

6.73 In some cases it may be necessary to appoint an acting or new CI or PI. The following guidance may be given to CIs, PIs and sponsors:

- Where the absence is likely to exceed 3 months or is indefinite, it is mandatory to appoint an acting or new CI or PI (see paragraphs 6.62 - 6.71).
- Where the absence is likely to exceed 4 weeks but will be less than 3 months, the sponsor should ensure that appropriate cover arrangements are made. The REC should be notified by letter about cover arrangements for absent CIs. R&D offices at NHS locations should be notified about cover arrangements for absent PIs.

If it has any concerns about the suitability of the arrangements, it should notify the sponsor. The REC has the discretion to request formal appointment of an acting CI or PI.

- For absences shorter than 4 weeks, it is not generally necessary to notify the REC.

6.74 The above guidance is not prescriptive. Other factors may need to be weighed, such as the nature, duration and progress of the research, the rate of recruitment and the structure of the research team.

6.75 Return of a CI or PI following a period of absence is not considered to be a substantial modification. The REC should be notified for information only of the return of a CI (in any study), or a PI in a CTIMP.

Urgent safety measures

6.76 The sponsor, Chief Investigator or any Principal Investigator may make changes to the conduct of a study for urgent safety-related reasons without first giving notice to the REC or obtaining a favourable opinion. Urgent safety measures are defined in the Clinical Trial Regulations, but the requirements apply to all types of research with a REC favourable opinion. Procedures relating to urgent safety measures are described in paragraph 10.10 - 10.13. For non-CTIMPs, the same procedure applies, but where the study was not reviewed by the MHRA (for example because it is not a study involving an IMP or device) then the references to notifying the MHRA are not relevant.

Modifications requested by the MHRA or REC (for CTIMPs only)

6.77 Under the Clinical Trial Regulations, the REC and MHRA can request that sponsors

modify their clinical trials. These requests will be made in cases where the REC is made aware of there being concerns regarding:

- the trial not complying with the principles and conditions of good clinical practice
- the safety of participants in the trial
- the scientific validity of the trial

6.78 If the REC receives concerns raised by a third party regarding an ongoing trial, it will initially contact the sponsor to notify them of the concerns and begin a discussion regarding the validity of the concerns raised. If the REC determine that a modification needs to be made, then a request will be sent to the sponsor representatives and the Chief Investigator.

6.79 The request will specify what modification needs to be made, the reason it's needed, and when it should be implemented. These requests for a modification will be sent at least 7 calendar days before the date the sponsor is expected to implement the change.

6.80 The number of days the REC will give for a change to be implemented will be proportionate to the complexity and scale of the proposed changes. If the sponsor has no objections to the modifications, or the timeframe in which they should be implemented, the sponsor should implement them per the instructions in the correspondence.

6.81 After implementing the modification the sponsor would also need to submit a substantial modification relating to it. The substantial modification submission would need to capture that the modification was requested by the MHRA or REC as well as the changes that were requested and made.

6.82 If the sponsor disagrees with the request for a modification (either the changes requested or the timeframe to implement them) they can make a written representation against it. The sponsor must submit this representation in writing to the MHRA or REC (whichever body issued the request for the modification) within 7 calendar days of receiving it. In the representation, the sponsor should explain their opposition to the modification and how they propose they will proceed.

6.83 Upon receiving the response, the MHRA or REC will confirm that they've received it. The MHRA or REC will then consider the points and, if necessary, inform the sponsor whether they should delay implementing the change so that they can consider it further. Once a decision is reached, they'll inform the sponsor of the outcome as

quickly as possible. If it's determined that the proposed modification does not need to be made, **or if a different timeframe for implementing it should be followed**, the sponsor will be notified of this and how they should proceed.

6.84 If, after reviewing the written representation from the sponsor, the MHRA or REC decide that the proposed modification is needed, the sponsor will be expected to implement it by a given date. The sponsor will also need to submit a modification after this to capture the change that has been made. The modification the sponsor submits should capture that it relates to a modification the MHRA or REC requested and be consistent with the changes the MHRA or REC requested be made.

6.85 If the MHRA and/or REC review a written representation provided by a sponsor and still agree the modification should be made the sponsor can appeal this. To appeal the decision the sponsor can do so by contacting appeals@hra.nhs.uk within 28 calendar days of receiving the email from the MHRA or REC informing them they should continue with implement the modification. In the email to us the sponsor should confirm their intent to appeal the decision.

Back to Contents

Section 7: Sub-committees

7.1 The Clinical Trials Regulations generally provide for the exercise of any of the REC's functions by a sub-committee consisting of members of the Committee.

Functions of sub-committees

7.2 The general guidance from RES is that the functions set out in paragraph 7.3 should normally be exercised by a sub-committee of the REC.

7.3 Sub-committees may exercise the following functions on behalf of the REC:

(i) Review of new applications submitted for proportionate review (see Section 4)

(ii) Review of substantial modifications relating to an application to which the REC has given a favourable opinion (see Section 6).

(iii) Reviewing responses provided by the applicant following a request for further information

(iv) Reviewing specialist advice provided by a referee when a request for further information pending specialist advice has been issued.

(v) Monitoring of research studies to which the REC has given a favourable opinion (see Section 10), including:

- Notifications of the conclusion of the trial or reports of early termination, and final study reports.
- Review of urgent safety measures taken by the sponsor.
- Review of serious adverse events (in the case of other research).
- Serious breach notifications.
- Referees' advice.

7.4 Sub-committee meetings may undertake a mix of the business listed in paragraph

7.5 It is not necessary to establish separate sub-committees, or arrange separate meetings, to undertake different types of business (where a sub-committee undertakes proportionate review of a new application, it is referred to in these SOPs as a "proportionate review sub-committee" for convenience).

7.6 A sub-committee should not undertake the primary review of a new application except where it is accepted for proportionate review.

7.7 Sub-committee business may be conducted, by video conference or by

correspondence between the members (see paragraphs 7.15 - 7.17). Consideration should be given to the significance of the matters to be discussed.

Authority of sub-committees

7.8 A sub-committee has delegated authority to take decisions on behalf of the REC on the matters listed in paragraph 7.3 above. Decisions taken by the sub-committee should not require ratification at the Committee meeting, unless the sub-committee specifically decides to refer a matter for further consideration and decision by the Committee. Decisions made by a sub-committee on behalf of the REC cannot be subsequently reversed by the REC.

Establishment of sub-committees

7.9 The REC may establish more than one sub-committee and may operate a mix of standing and ad hoc sub-committees.

Quorum for meetings

7.10 The quorum for sub-committee business (excluding Proportionate Review) is the Chair or vice-Chair of the relevant REC (or, if neither is available, the Alternate Vice-Chair) and at least one other member. It is desirable but not essential for a health or social care member to be involved.

7.11 The appropriate member of Approvals staff/REC Manager is responsible for ensuring that appropriate expertise is available to any sub-committee, depending on the business to be undertaken.

Distribution of documents

7.12 Documents for sub-committee meetings should normally be made available no later than 3 calendar days prior to the meeting.

Submission of written comments prior to meetings

7.13 With the exception of sub-committees held via correspondence, a member who is unavailable to attend a sub-committee meeting may submit comments in writing on any agenda item prior to the meeting. These may be tabled at the meeting at the discretion of the Chair. Where minutes are taken, they should record the submission of written comments as per paragraph 2.38. Attributable comments should not be uploaded to HARP.

7.14 A member who submits written comments but does not attend the meeting either in

person or on the telephone does not count towards the quorum.

Conduct of sub-committee business by correspondence

7.15 Sub-committee business is usually conducted by correspondence. The Approvals Administrator/REC Manager should list the business in an email to the members concerned and make the documents available in the Member Portal with deadlines for receipt of comments. A separate agenda document is not required in this case.

7.16 Where business is conducted by correspondence, the Chair is responsible for reviewing any comments made by other members and for making decisions on behalf of the REC. Telephone discussions or a teleconference or videoconference may be held between the Chair and the members involved. Where there are differences of view among members, these may be discussed further at a meeting of the sub-committee or the Committee, at the discretion of the Chair. Records should be kept of the comments of all members concerned until the minutes have been ratified, if appropriate, and then all original records should be destroyed (see paragraph 15.8). Attributable comments should not be uploaded to HARP (comments entered in the member portal are deleted automatically 30 calendar days after the final opinion has been issued).

7.17 Where applicable, minutes of the business (such as minutes for breaches, expert opinion, or where the REC is notified of a USM) should be prepared by the Approvals Administrator/REC Manager. All decisions made in correspondence should be recorded in the next REC Report (see paragraphs 2.13 - 2.18).

Attendance of investigators

7.18 Investigators are not normally invited to sub-committee meetings. However, exceptionally the REC may invite the Chief Investigator, local Principal Investigator or sponsor's representative for a research study to attend a sub-committee meeting where this would be helpful in providing further clarification, resolving issues of concern to the REC and reaching an early decision.

Referees

7.19 Specialist referees may be invited to submit written advice prior to a sub-committee meeting, or to attend the meeting in person, in the same way as for a REC meeting. The procedures set out in paragraph 2.43 should be followed.

Observers

7.20 The procedures for attendance of observers at REC meetings (see paragraphs 2.55 - 2.60) also apply to sub-committee meetings.

Responsibilities of Staff

7.21 The responsibilities of the staff in relation to sub-committee business are:

(i) Distributing papers to members and specifying dates for written comments to be returned

(ii) Recording attendance/participation by members and referees at meetings.

(iii) Co-ordinating correspondence and arranging for written comments to be reviewed by the Chair if required.

(iv) Advising meetings as necessary on compliance with standard operating procedures.

(v) Following up the decisions taken as appropriate.

(vi) Where applicable, preparing minutes of the business e.g. serious breaches, urgent safety measures, serious adverse events, review of expert referee advice (see paragraph 7.17).

(vii) Issue the decision letter as appropriate

Minutes of sub-committee meetings

7.22 The requirements of paragraphs 2.68 would also be applicable to sub-committee meetings where minutes are required, in the same way as for REC meetings.

7.23 Where applicable, minutes of sub-committee meetings should be ratified by the members who were present. This may be done by correspondence or at a subsequent meeting of the sub-committee or full committee. Following ratification, the minutes should be signed and dated by the sub-committee Chair and by the Approvals Administrator/REC Manager or REC Assistant.

7.24 The minutes of sub-committee meetings are confidential, and paragraph 2.80 applies in the same way as for REC meetings.

7.25 The REC should be notified of the decisions taken by sub-committee (see paragraphs 2.13 - 2.18).

Back to Contents

Section 8: Further review of research given an unfavourable opinion

Options available to the applicant

8.1 Where a REC has given an unfavourable opinion on an application for ethics review, the applicant has the following options for seeking further review:

(i) The applicant may submit another application, which should be reviewed as a new application (paragraphs 8.2 - 8.8);

(ii) The applicant may appeal against the decision of the first REC and seek a second opinion from another REC on the same application ("the second REC") (paragraphs 8.11).

(iii) Request may be made to vary the opinion where it appears to be based on error or misunderstanding (see paragraphs 3.51 - 3.55). When the opinion is varied, the clock should remain stopped from when the original opinion was issued until the error or misunderstanding is resolved. The clock should then be corrected accordingly.

Submission of a new application

General procedures for review of new applications

8.2 It is open to the applicant to submit a new application relating to the same research proposal. The assumption should be that the applicant is attempting to address the concerns raised by the REC that rejected the previous application. For applications not submitted via combined review service, the applicant can duplicate the original application form in IRAS and amend to incorporate the relevant changes. It should be clearly indicated on the application form that it relates to a research proposal that has been previously reviewed and should cite the REC reference number. If it comes to light that an applicant has failed to declare this, the Chair should consider reporting the matter to the Operational Manager (see paragraphs 10.42 onwards).

8.3 A new application should be booked and electronically submitted. The application will receive a new REC reference number. The validation procedures in Section 1 apply. In addition to the usual validation criteria, the following requirements:

- A covering letter has been provided, explaining how the new application addresses the reasons given for the unfavourable opinion.
- A copy of the unfavourable opinion letter should be provided.

- Any changes to study documents have been highlighted, and documents given revised version numbers and dates where applicable.

8.4 The application should be ethically reviewed according to normal procedures.

8.5 Where the application is being reviewed by a different REC, the Approvals Specialist/REC Manager of the second REC can obtain any of the original documents or correspondence relating to the previous review from HARP. All relevant correspondence should be included with the documentation submitted to members for review at the meeting.

Booking and submission of new applications

8.6 It is highly desirable that the new application is re-booked with the original REC, as the members will already be familiar with the issues relating to the research and well placed to evaluate the changes made to the application. However, the applicant is entitled to apply to another appropriate REC if they preferred, except where the first REC is the only REC with the legal authority to review the application (see paragraph 1.11).

8.7 If there is a risk that the final opinion may not be issued by the original REC within 60 calendar days, the resubmission should be booked for review by a different REC. Circumstances which may affect the final decision being issued by the original REC within 60 calendar days may include the following:

- The application is going to be received more than two weeks ahead of the REC's next closing date.
- The agenda for the next meeting of the REC is full.
- The next meeting of the REC will need to be cancelled due to a risk that it may not be attended by enough members.

8.8 Review by a different REC should take place only with the Chief Investigator's agreement. If the Chief Investigator is content to wait for an agenda slot at the original REC, the validation date will be the closing date for submissions to the next available meeting.

Vexatious applications

8.9 An applicant or different applicants may in principle continue to submit new applications relating to the same research proposal. However, following review of three applications (including any withdrawn applications after review), the procedure for declaring an applicant to be vexatious may be invoked if:

- There is no reasonable possibility of the applicant being able to address the concerns raised by the committee(s) that gave an unfavourable opinion, or
- The applicant does not appear to be making a genuine attempt to understand or address the concerns, or their behaviour is in any other way vexatious, and
- Further review of the project would serve no useful purpose and would be a waste of members' time and public resources.

8.10 Procedures for declaring an applicant to be vexatious are as follows:

(i) The Chair of any REC that is in the process of reviewing, or has reviewed, an application may raise concerns with the Operational Manager (through the Approvals Specialist/REC Manager) based on the grounds in 8.9.

(ii) The Operational Manager should investigate the application history in consultation with the Chair and Approvals Specialist/REC Manager of the REC most recently involved in review of the project and, if appropriate, with other RECs concerned.

(iii) If it is considered that the criteria in paragraph 8.9 apply, a recommendation should be made to the Deputy Director of Approvals Service to declare the applicant vexatious.

(iv) The Deputy Director of the Approvals Service will consider the recommendation in consultation with the Head of Approvals Operations. If it is endorsed, review of any outstanding application should cease. Any subsequent correspondence or enquiry from the applicant, or any further applications, should be redirected to the Head of Approvals Operations, who should also notify the applicant in writing that any further correspondence or new applications should be sent direct to him/her.

(v) On receipt of any further correspondence or a new application, the Head of Approvals Operations will consult the Chair of the REC that most recently rejected an application from the applicant ("the last REC"). A valid new application not related to the previous project should be accepted for review and centrally allocated to an appropriate REC. If the application relates to the same project, and it appears that the ethics issues raised previously may have been addressed, the application may be allocated to the last REC. If in the opinion of the Chair no attempt has been made to address the issues, the unfavourable opinion for the previous application should be re-issued and no further review will take place.

Appeals: statutory provisions and general policy

8.11 Where a recognised REC has given an unfavourable opinion on a CTIMP, the Clinical Trials Regulations allow the Chief Investigator (except where paragraph 8.12 applies) to send a written notice to UKECA stating that they wish to appeal against the opinion and making representations. Such notice must be given within 90 calendar days (14 calendar days for a gene therapy or advanced therapy CTIMP) of being notified of the unfavourable opinion of the first REC, but UKECA may extend this period in a particular case. UKECA may then direct that the application should be reviewed by another recognised REC. It may refuse to issue a direction if it considers that the grounds for appealing against the opinion are unfounded. If so, a notice should be sent to the Chief Investigator setting out the reasons for refusal.

8.12 The Clinical Trials Regulations specifically exclude provision for appeal where a CTIMP involving adults with incapacity in Scotland has been given an unfavourable opinion by the "designated committee" under the Adults with Incapacity (Scotland) Act 2000.

8.13 The policy of the Department of Health and Social Care and the devolved administrations is that RES should exercise the functions of UKECA relating to appeals. The procedures for appeals apply to any research reviewed by a REC in the UK under these SOPs, except where paragraph 8.12 applies.

Appeal procedures

Notice of intention to appeal

8.14 When issuing an unfavourable opinion on an application, the REC should notify the applicant of the procedures for giving notice of an intention to appeal and the appropriate contact points.

8.15 Notice of intention to appeal should be given in writing within 28 calendar days of the date of the letter confirming the unfavourable opinion of the first REC, unless in exceptional circumstances agreed with the Appeal Manager. The notice may include representations with respect to the opinion of the first REC. The applicant may not make changes to the application or supporting documentation but may provide details of changes they agree to make in the notice of intention to appeal. Appeals will normally be accepted, though RES reserves the right to disallow an appeal.

8.16 Notice should be given by the applicant in writing to the Appeal Manager. The Appeal Manager should then make arrangements to allocate the application to another REC

for review, taking into account any legal or regulatory requirement for review by a particular REC, and for an agenda slot to be booked at its next meeting.

8.17 The Appeal Manager has the discretion to accept a notice of intention to appeal given after 28 calendar days has elapsed, taking account of any exceptional circumstances.

8.18 Where a request to appeal is allowed, the Appeal Manager will upload the Appeal Request to HARP via the 'checklist' tab. The application should then be transferred as an appeal via HARP to the second REC.

8.19 The Appeal Manager should notify the Chief Investigator by email whether the appeal is allowed. The email should state which REC has been allocated to review the application, the date of the meeting at which it has been booked and the new REC reference number. Copies will be sent to the Approvals staff/REC Managers of both RECs. Where the appeal is disallowed, the Appeal Manager should email the Chief Investigator giving reasons. Copies will be sent to the REC email address.

8.20 The validation date for the appeal will be the date of the letter to the applicant confirming that the appeal is allowed; where the first meeting offered is accepted by the applicant. If the first offered meeting is not accepted, the validation date will be the cut-off date for the meeting which is accepted. At the request of the Chief Investigator, the Appeal Manager may agree to defer the appeal to a later meeting of the second REC, for example to allow the CI to attend the meeting or make other preparations for the appeal. If the appeal is deferred, the validation date will be the submission date for the meeting at which the appeal is booked.

Preparation for the appeal

8.21 The applicant is not permitted to make any revision to the application reviewed by the first REC.

8.22 If the first REC gave an unfavourable opinion at the REC meeting, without a request for further information, the documentation sent to the second REC should be that originally submitted to the first REC. If the unfavourable opinion was confirmed at a later stage of the process, and the documentation was revised in response to a request for further information, then the latest versions should be submitted to the second REC.

8.23 Once the appeal has been correctly managed on HARP a copy of the application will be received by the second REC. The application does not need to be re-entered on HARP. There is no requirement for the normal validation letter to be sent but the

Chief Investigator should be provided with the details for attending the meeting.

8.24 The applicant may submit additional representations to the second REC by the specified closing date. In this context, “representations” means observations with respect to the opinion of the first REC, not changes to the application or supporting documentation.

8.25 When sharing the documentation to members prior to the meeting, the Approvals staff/REC Manager of the second REC should include a copy of the correspondence relating to the application and any representations submitted by the applicant.

8.26 The Approvals staff/REC Manager of the second REC should invite the Chief Investigator to the meeting. It is particularly important that the Chief Investigator attends the meeting if possible so that a full discussion can take place on the main ethics issues.

Review of applications on appeal

8.27 The application should be reviewed by the second REC in accordance with the standard procedures for review of any new application.

8.28 The second REC may consider the matters raised by the first REC in the course of the review but is not bound by them. It should consider carefully any representations made by the applicant.

8.29 If the second REC gives a favourable opinion of the application, this supersedes the opinion given by the first REC. The second REC assumes all further responsibility for monitoring the research and reviewing substantial modifications.

8.30 If the second REC gives an unfavourable opinion, there is no provision for any further appeal relating to this application. The letter issuing an unfavourable opinion should be amended to omit reference to any further appeal. The applicant may however submit a new application relating to the same research proposal (see paragraph 8.2), suitably revised to take account of the ethical concerns raised. If so, the application should normally be reviewed by one of the RECs that reviewed the previous application.

8.31 The second REC should copy all correspondence on its review, including the outcome, to the first REC.

Back to Contents

Section 9: Expedited Review

General policy

9.1 There is no statutory provision for the expedited review of applications. The Clinical Trials Regulations provide only that a REC shall give an opinion on any valid application within a period of 60, 90 or 180 calendar days (depending on the type of trial), which may be suspended once pending receipt of further information from the applicant (see paragraphs 3.1 - **Error! Reference source not found.**).

9.2 However, the REC Policy Document recognises that some research may be suitable for expedited review, for example, research undertaken in a public health emergency.

9.3 The Research Ethics Service aims to facilitate such research by expediting the review process and adopting a proportionate approach to the ethics review.

9.4 There may be exceptional circumstances where, as a matter of public policy and in the national interest, it is essential that an application should be reviewed urgently to allow the study to commence as quickly as possible.

9.5 Along with other relevant regulators, the Research Ethics Service will adopt the following criteria when considering whether expedited review of research is warranted:

- The time available to complete the approvals process and initiate the research.
- The potential loss of valuable data or data quality, or disproportionate effort being required to capture the data.
- The potential impact of any delay on public health.
- The importance of the research for informing, shaping or defining health policy and service provision.

9.6 Where a research sponsor or Chief Investigator believes that such circumstances may apply, they should contact the Deputy Director of Approvals Service and/or the REC operational manager in Scotland, Wales or Northern Ireland (as applicable) directly for advice. The Approvals staff/REC Managers or Chairs of individual RECs have no authority to expedite or set aside the normal procedures for ethics review in such cases.

9.7 For studies taking in place in England, including those with locations in another UK country, the Deputy Director of the Approvals Service, or a nominated deputy, will consider the request against the criteria in paragraph 9.5 and in consultation with

other relevant operational managers as appropriate. For studies taking place in Scotland, Wales or Northern Ireland, requests will be considered by the REC operational manager in the country concerned. Where the relevant manager considers that the circumstances justify it, the sponsor or Chief Investigator may be given permission to submit an application for expedited review. Other regulatory and review bodies will be informed of the decision. The applicant will also be notified of relevant contact points in case they wish to make similar requests to other bodies.

9.8 An application for expedited review may be submitted by either the sponsor or the Chief Investigator of the proposed research. The standard IRAS application form should be used, and all the usual supporting documentation should be provided.

9.9 The Deputy Director of Approvals Service should arrange for review of the application in one of the following ways:

(i) An existing REC may be appointed to review the application. The Deputy Director of Approvals Service may arrange for two members of other RECs with relevant expertise to be co-opted to the REC, and/or for other experts to be specially appointed as members of the REC for the review of this application.

(ii) A new REC may be established by RES specifically for the review of this application. If the application relates to a CTIMP, the REC will need to be legally recognised by UKECA. The membership of the REC will be a matter for the discretion of the Deputy Director of the Approvals Service but should include both lay members and relevant experts. A Chair and appropriate Approvals staff/REC Manager should be appointed by the Deputy Director of the Approvals Service.

9.10 The Deputy Director of Approvals Service or Head of Approvals Operations will advise the applicant directly on the arrangements and oversee the process throughout to ensure the application is reviewed as expeditiously as possible compatible with robust review of any material ethical issues raised by the research. The REC appointed to review the application (“the appointed REC”) should do so following standard operating procedures, except that the Deputy Director of Approvals Service or Head of Approvals Operations may specify the time periods within which each stage of the process should be completed.

9.11 For CTIMPs, investigations of medical devices, and combined CTIMP and medical device studies, the sponsor or Chief Investigator should provide the appointed REC with appropriate evidence of the arrangement to assess suitability of locations, investigators and facilities. The Chair or Approvals staff/REC Manager of the

appointed REC may consult relevant RECs or other organisations for advice.

9.12 Where a favourable ethics opinion is given by a specially appointed REC under paragraph 9.9(ii), and that REC is later abolished, the Deputy Director of Approvals or Head of Approvals Operations Service should re-assign the responsibilities for monitoring the research and reviewing modifications to another REC.

Back to Contents

Section 10: Monitoring of research given a favourable opinion

Statutory requirements

10.1 Under the Clinical Trials Regulations, the sponsor of a clinical trial of an investigational medicinal product has a variety of statutory responsibilities for notifying the REC of developments in the research after it has started. These are set out in this section, with the exception of provisions relating to substantial modifications (see Section 6). Where there is more than one sponsor, "the sponsor" refers to the sponsor that has been designated to take responsibility for the function concerned. A single sponsor should take responsibility for each of the following:

- notification of urgent safety measures,
- pharmacovigilance and safety reporting,
- notification of the conclusion or early termination of the trial. This includes when a trial is ended due to lack of recruitment in the UK (see paragraph 10.5).

General policy on monitoring of research

10.2 The REC should keep under review the favourable ethics opinion given to any research study in the light of any significant developments in the research.

10.3 The REC has no responsibility for proactive monitoring of research studies. The accountability for this lies with the sponsor and the employing organisation.

10.4 The Chief Investigator and representatives of the sponsor may be requested to attend a meeting of the REC or sub-committee at any time to discuss any ethical or safety concerns about the research.

Commencement of the research

10.5 All CTIMPs are expected to recruit their first participant in the UK within 2 years of the trial being approved. If no participants are recruited in the UK within 2 years, then the approval for the trial will lapse. The sponsor should end the trial and submit notification in writing by the date that the approval lapses. Continuing to run a CTIMP after the approval has lapsed would be considered an offence under the Clinical Trial Regulations. Sponsors are able to request an extension to the 2 year timeframe by contacting the MHRA.

10.6 For non-CTIMPs, it is expected that the research should commence within 12 months

of the date on which a favourable ethics opinion is given by a REC. A study is generally considered to have commenced when any of the procedures set out in the protocol are initiated. Should the study not commence within 12 months; the Chief Investigator should give the REC a written explanation for the delay. Should the project not commence within 24 months; a further explanation should be given. The REC may review its opinion under the procedures in paragraphs 10.72 - 10.92.

10.7 If a study is abandoned prior to commencement, the Chief Investigator or sponsor should notify the REC (and, in the case of a CTIMP, the MHRA) by letter, giving reasons. It is not necessary to submit the form for declaring the conclusion or early termination of the study (see paragraphs 10.61 - 10.71). If a study is abandoned and it is later proposed to start it afresh, a new application should be made. For global CTIMPs, if the trial has commenced in any participating nation, the process set out in 10.61 should be followed even if the trial has been abandoned in the UK.

Duration of a favourable ethical opinion

10.8 The favourable ethics opinion of the REC for a specific research study applies for the duration of the study, except where action is taken to suspend or terminate the opinion (see paragraph 10.72 onwards). Extension of the study period is not in itself a substantial modification, except where it is related to other modifications that would be substantial, such as an increase in target recruitment, addition of new procedures or sub-studies, or extension of follow-up. Where the duration of the study is to be extended beyond the period specified in the application form, the REC should be notified.

10.9 In England, Wales and Northern Ireland, samples may be held without a HTA license after the end of study date has been reached, for verification or quality checking of the research data. This should be detailed in the protocol which is approved by the REC and should be for no longer than 12 months. After this period legal authority to hold any human tissue under the ethical approval for this project will expire. To ensure that any continued storage is lawful, either the tissue must be held on premises with a storage licence from the Human Tissue Authority, or an application made for ethical review of another project before the favourable ethics opinion (including the additional time after the declaration of the end of study, if applicable) of the existing project expires. Otherwise, the tissue would need to be destroyed in accordance with the HTA Codes of Practice. If additional time is needed to undertake the main analysis, then the REC should be informed of this before the end of study is declared.

Urgent safety measures

10.10 The Clinical Trials Regulations provide that the sponsor or the Chief Investigator, or the local Principal Investigator at a trial location, may take appropriate urgent safety measures in order to protect the participants of a CTIMP against any immediate hazard to their health or safety. Although urgent safety measures (USMs) are defined in the Clinical Trial Regulations, the requirements apply to all types of research with a REC favourable opinion. For studies that were not reviewed by the MHRA (for example because it is not a study involving an IMP or device) the same procedure set out below should be followed but notification to the MHRA is not required. For USMs, the REC and the MHRA must be notified within 7 calendar days that such measures have been taken and the reasons why. The policy from RES is that these requirements should apply to all other research with a favourable opinion from a REC. For trials which have been approved via the CTIMP combined review service, one USM notification is made via IRAS and received by the MHRA. No additional notification is required directly to the REC – the REC notification will be via the substantial modification which follows the USM notification.

10.11 The initial notification to the REC should be in writing and should be sent within 7 calendar days (this does not apply for trials approved via the CTIMP combined review service where the notification is made through IRAS). The notice should set out the reasons for the urgent safety measures and the plan for further action.

10.12 Where an urgent safety measure requires a modification to study documentation such as the participant information sheet or consent form, this should be submitted as a substantial modification to the REC as soon as it is possible to do so. The substantial modification should be marked as being in response to urgent safety measures and a copy of the urgent safety measure notification submitted with the substantial modification. The REC will aim to give a formal opinion on the substantial modification within 28 calendar days but will give an opinion, or request further information, in no more than 35 calendar days.

10.13 The REC is not required to approve urgent safety measures prior to implementation. However, notifications of urgent safety measures should be reviewed at a meeting of the REC or sub-committee. The REC should consider whether the measures taken are appropriate in relation to the apparent risk to participants, and what further action the sponsor and investigator(s) propose to take, for example, the submission of modifications to the protocol. Where any concern arises about the safety or welfare of participants or the conduct of the research, the REC should address these with the

sponsor or Chief Investigator in writing.

Safety reporting in clinical trials of investigational medicinal products

10.14 The MHRA website provides guidance on the collection, verification and reporting of safety events which occur in a clinical trial falling within the scope of the Clinical Trials Regulations. The MHRA guidance describes the requirements for safety reporting by the investigator to the sponsor, and by the sponsor to the REC. The following paragraphs summarise the key requirements as they apply to reporting to ethics committees.

Expedited reporting of individual SUSARs in the UK

10.15 Suspected Unexpected Serious Adverse Reactions (SUSARs), which are associated with the use of an investigational medicinal product (IMP) in the trial, must be notified to the MHRA only - The MHRA will liaise with the REC if deemed appropriate. This includes SUSARs associated with an active comparator drug used in the trial. Where RECs receive reports of SUSARs, these should be confidentially destroyed and there is no requirement to acknowledge receipt.

10.16 The protocol and REC application form should provide the REC with an up-to-date summary of the safety profile. Where the sponsor subsequently receives safety data during the ethical review process or prior to the start of the trial in the UK, which materially changes the safety profile of the IMP as described in the REC application and could affect the risk/benefit assessment and information to be provided to potential participants, this should be notified to the REC.

10.17 An adverse event associated with placebo will not normally satisfy the criteria for a SUSAR. If this occurred exceptionally (e.g. a reaction due to an excipient or impurity) it should be reported. This guidance also applies to safety reporting of other research (10.29 - 10.32)

10.18 If a Serious Adverse Event has occurred in a CTIMP but the SAE is not related to the Investigational Medicinal Product(s) (IMP), this would not meet the definition of a SUSAR and does not need to be reported to the. It would be expected that where the event is related to a licensed non-investigational medicinal product (NIMP), the manufacturer of the non-IMP is informed of any significant safety findings and use of the yellow card scheme is encouraged. If there is any question that the unexpected SAE could be due to the IMP, then it should be reported to the MHRA as a SUSAR for the IMP. All events should be recorded in the Case Report Form/study

documentation regardless as to whether they were related to an IMP or to the non-IMP treatment.

Other expedited safety reports

10.19 Events may occur during a clinical trial that may be relevant to participant safety and require action to protect participants but do not meet the definition of a SUSAR. These include:

(a) an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,

(b) a new event, related to the conduct of the trial or the development of the IMP, that is likely to affect the safety of participants, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial (for example a SAE occurring during the run-in period),
- a significant hazard to the participant population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study (such as carcinogenicity),
- any anticipated end or temporary halt of a trial for safety reasons where the trial is conducted with the same IMP by the same sponsor in another country.

(c) the conclusions or recommendations of a data monitoring committee, where relevant for the safety of participants.

10.20 These events/observations are not to be reported as SUSARs but might require other action such as urgent safety measures, substantial modifications or early termination of a trial. Where such actions are not taken, it is recommended that the sponsor informs competent authorities and ethics committees of any safety issues which might materially alter the current risk/benefit assessment of the IMP.

Annual safety reports

10.21 For each IMP being tested in the trial, the sponsor should provide the MHRA with an annual report on the safety of participants, in all clinical trials of the product for which the sponsor is responsible, whether in the UK or elsewhere. The annual safety report does not need to be submitted to the REC. It should be submitted by the applicant

via IRAS to the MHRA only. Where there is action taken by the sponsor in relation to information contained in the annual safety report, this will require the sponsor to submit a substantial modification and the REC will be informed via this route. The reporting requirement ends when the conclusion or early termination of the trial has been notified in the UK (even if the trial is continuing in other countries).

Responsibilities for monitoring the safety of clinical trials

10.22 The primary responsibility for monitoring the safety of research participants lies with the trial sponsor. For certain kinds of CTIMP; trials with predicted high morbidity or mortality, or double-blind trials with unknown or uncertain risks; sponsors are strongly encouraged to establish an independent Data Monitoring Committee (DMC) to advise on safety issues. The sponsor has a duty to take action, which may include urgent safety measures, protocol modifications or even the suspension or termination of a trial, where the safety profile or the risk/benefit analysis changes significantly.

10.23 Sponsors are required to submit complete data on all SUSARs in accordance with guidance published by the MHRA. In the UK regulatory context, the MHRA will actively monitor the safety of clinical trials. Where the MHRA raises safety concerns with the sponsor, it will directly inform the REC so that any implications for the ethics of the trial can be considered in parallel.

10.24 In this context, the responsibilities of the REC are inevitably more limited. RECs do not have access to comprehensive safety data (in particular, SUSARs outside the UK are not subject to expedited reporting to the REC), nor do they generally have the resources and expertise required to carry out in-depth analysis of the available data. The REC should, however, be ready to act on safety concerns that are brought to its attention by the sponsor or the MHRA. In particular, the REC is responsible for ensuring that the consent of participants continues to be based on accurate and up-to-date information about risks and benefits.

10.25 The REC should therefore review safety reports in accordance with the following guidance.

Review of safety reports by the REC

10.26 Where concerns arise about SUSARs, DMCs or safety reports, the MHRA may liaise with the REC if deemed appropriate. Where concerns are raised and the REC requires further information, the Chair may write to the Chief Investigator or sponsor to express its concerns and may request further information. The correspondence should be copied to the Head of the Clinical Trials Unit at the MHRA by email (see

paragraph 14.9). The Chief Investigator may be requested to attend a meeting of the sub-committee or Committee to discuss the concerns of the REC.

Communications with MHRA on safety issues

10.27 The REC should draw the attention of the MHRA to any substantial concerns about the safety of trial participants, the accuracy of the risk/benefit analysis or the need for new information to be given to participants. Communications should be sent to the Head of the Clinical Trials Unit by email ctdhelpline@mhra.gov.uk (see paragraph 14.9). The correspondence will be acknowledged.

10.28 Where the MHRA has concerns about the safety of trial participants or there is a change in the risk/benefit analysis, it will keep the REC informed of any action it takes. The Head of CTU will ensure that any relevant correspondence with the sponsor is copied to the REC. The REC may seek further information or clarification from the Head of CTU. It may also recommend that the CTU takes action in relation to the CTA, for example to request modification of the participant information sheet.

Safety reporting for other research

10.29 In research other than CTIMPs, a Serious Adverse Event (SAE) is defined as an untoward occurrence that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.

10.30 An SAE occurring to a research participant should be reported to the REC where in the opinion of the Chief Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

10.31 Reports of related and unexpected SAEs should be submitted within 15 calendar days of the Chief Investigator becoming aware of the event, using the SAE report

form for non- CTIMPs published on the HRA website.

10.32 Individual reports of SAEs should be reviewed at a sub-committee or REC meeting. The purpose of the ethics review is to check the accuracy of the risk/benefit analysis as described in the participant information sheet and to consider the possible need for new information to be given to participants and their consent sought to continue in the study if necessary. The REC should also consider any other issue that may be relevant to the ethics of the trial.

Protocol/GCP Compliance and Serious Breaches

Protocol Violations

10.33 Protocol violations are non-compliances in relation to the protocol resulting from error or fraud/misconduct and identified, for example, through the sponsor's monitoring or inspection by regulatory bodies.

10.34 The primary responsibility for investigating protocol violations and taking corrective action lies with the sponsor. It is not necessary for sponsors to notify the REC of very minor protocol violations unless they constitute a 'serious breach' or 'protocol violation' requiring particular changes to the study (e.g. protocol changes, participant facing material changes). Where a sponsor voluntarily notifies the REC of a very minor protocol violation the REC staff should acknowledge receipt and send the report to the Chair and to breaches@hra.nhs.uk for information. There is no need for any further action unless the Chair or the Quality and Performance Manager considers that the violation, taken alone or in combination with other reports of minor violations, should be treated as a serious breach.

10.35 If the Chair considers the minor protocol violation to be a serious breach or a protocol violation requiring review, then the breach should be re-classified and reviewed by either a subcommittee or a full committee and the process for the review of serious breaches/protocol violations should be followed.

10.36 The outcome to rectify a serious breach, and sometimes a protocol violation, is often through the substantial modification process, this allows the REC/Sponsor to have a process to follow and also ensures any relevant paperwork or processes are amended to ensure that the breach does not re-occur. This also supports (where applicable) multi centre research projects ensuring all locations are following the exact same revised paperwork/processes as applicable to rectify the reported breach and prevent any reoccurrence.

10.37 When the Chair/Sub Committee reviews a reported protocol violation, further information may be requested from the sponsor and further action may be suggested; but in most cases the breach will just be noted and closed as in most cases the Chair/Sub Committee will be satisfied with the information within the breach reporting document regarding what corrective action has taken place.

Serious breaches of the protocol or GCP

Reports by the sponsor

10.38 A “serious breach” is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the research.

10.39 The sponsor should notify the REC and relevant regulatory bodies of a serious breach in any study within 7 calendar days of the matter coming to their attention. The report may be provided by the Chief Investigator or other representative of the sponsor, copied to the sponsor.

10.40 In the case of a CTIMP, the sponsor is required by the regulations to notify the MHRA of a serious breach within the above timeline. The report form prescribed on the MHRA website should be used and a copy provided to the REC.

10.41 Reports of serious breaches should give details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given, and the REC informed what further action the sponsor plans to take. Any such report should be considered at a meeting of the REC or by a sub-committee. In circumstances where consideration by the REC is no longer appropriate, for example where the study has closed, any reports provided may be referred to the HRA breaches@hra.nhs.uk for consideration. Where consideration is given by the REC to reviewing the opinion, either for the whole of the UK or at an individual location, the REC should follow the guidance in paragraphs 10.72 – 10.92. The matter should be reported to the Quality and Performance Manager in line with the guidance published separately.

Other reports of possible serious breaches

10.42 Where a REC receives information other than from the sponsor (or sponsor’s representative) suggesting that a serious breach may have occurred in relation to an application for ethics review or the conduct of research, the information should be emailed to breaches@hra.nhs.uk.

10.43 The relevant staff member should send the details of any possible serious breaches received to breaches@hra.nhs.uk.

10.44 It will be for the Quality and Performance Manager to decide whether the information should be shared with other bodies so that the matter can be formally investigated if appropriate. Consideration should be given to notifying the following:

- The research sponsor.
- The researcher's employer.
- The Chief Executive and R&D Director for any relevant NHS care organisation(s).
- MHRA GCP Inspectorate (CTIMPs only – see paragraph 14.14 - 14.20).
- MHRA (Devices*)* (clinical investigations of medical devices only – see paragraph 14.37).
- Other regulatory bodies where applicable.

10.45 The Quality and Performance Manager and relevant RECs should be kept fully informed of any action taken. Where insufficient information is available in respect of a reported potential serious breach, it will be open to the Quality and Performance Manager to bring the matter to the attention of the Head of Approvals Operations.

10.46 The HRA, as the Appointing Authority for RES RECs, may write to any of the bodies listed above to request further information in relation to the matter.

10.47 It is for the REC to consider whether any action needs to be taken in relation to the ethics opinion for the research, where there could be an immediate risk to the safety of participants. The REC may review the favourable ethics opinion for the study or for a particular location (see paragraphs 10.72 and 14.22 - 14.25). The opinion on a non-CTIMP may be suspended pending the outcome of further investigation by other bodies. Such a decision should only be taken after careful consideration of the implications for research participants already recruited.

10.48 A member of a REC who becomes aware of a possible serious breach should report this to the Chair and Approvals staff/REC Manager, who will be responsible for reporting the matter in accordance with paragraph 10.42.

10.49 Receipt of information under this section includes any report from a member of an investigator's team of alleged fraud or misconduct.

10.50 Further operational management guidance about reporting and follow-up of possible

serious breaches is issued by the Quality and Performance Manager.

Criminal offences

The Clinical Trials Regulations create a variety of criminal offences relating to contravention of its provisions. Offences under the Clinical Trial Regulations include:

10.51 commencing or conducting a CTIMP without it receiving both a favourable ethics opinion from a recognised REC and a Clinical Trial Authorisation.

10.52 implementing a substantial modification to a CTIMP without a favourable ethical opinion,

10.53 failure to notify the REC of urgent safety measures or the early termination or conclusion of the trial

10.54 providing false or misleading information to a recognised REC in the course of an application (or modification) for an ethics opinion relating to a CTIMP.

10.55 Failure to register the trial or publish results of the trial, as per the requirements set out in the Clinical Trial Regulations (see paragraphs 3.19 - 3.23)

Where a REC receives information suggesting that a criminal offence may have been committed, it should proceed as in paragraph 10.22.

Good Clinical Practice inspections

Co-operation with investigations

10.56 Requests to provide information or assistance in connection with investigations by other bodies into serious breaches or other suspected fraud or misconduct should be referred initially to the HRA. With the permission of an operational manager, the REC should co-operate fully. The REC should not under any circumstances undertake its own investigations.

10.57 The REC should co-operate fully if asked to assist with criminal investigations. The Deputy Director of Approvals Service should be kept informed.

Temporary halt of the research

10.58 When the sponsor halts a CTIMP temporarily (whether it is a halt of the whole trial or at individual trial locations), the MHRA and REC should be notified within 15 calendar days by a substantial modification (see paragraph 6.2). The modification should clearly explain the reasons for the halt and the scope, e.g. stopping recruitment and/or interrupting the treatment of participants already included. The substantial

modification should be reviewed by the REC in the normal way.

10.59 To restart the trial, the sponsor should submit a further substantial modification requesting authorisation and a favourable ethics opinion. Evidence should be provided that it is safe to restart the trial. If the sponsor decides not to recommence the trial after a temporary halt, the conclusion of the trial should be declared (see paragraph 10.62).

10.60 The same procedures apply to the temporary halt of any other research in order to protect participants from harm.

Declaration of the conclusion or early termination of the research

10.61 The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the REC in writing that a CTIMP has ended within 90 calendar days of the conclusion of the trial. In the case of an international trial, the sponsor is only required to notify the conclusion of the trial as a whole. Where the UK arm of a trial ends in advance of the conclusion in other countries, this may be notified voluntarily (the form for declaring the end of the trial can be used in this case).

10.62 If the trial is terminated early, the sponsor should notify the REC within 15 calendar days of the date of termination. An explanation of the reasons for early termination should be given. If the trial has been terminated early for safety reasons it should be registered with immediate effect even if a registration deferral has been allowed by the HRA (see paragraphs 3.19 - 3.23).

10.63 The definition of the conclusion of the research should be provided in the protocol and any change to this definition should be notified as a substantial modification. The end of the research should be defined in relation to the collection of all data required to answer the research questions in the protocol. For studies involving human tissue, the analysis of the samples should be undertaken as part of the data collection before the end of study is declared. Where a clinical trial protocol requires follow-up monitoring and data collection to meet secondary or tertiary endpoints, the end of trial should be the final data capture rather than the last treatment visit.

10.64 Declarations of the conclusion or early termination of a CTIMP should be in the form available on the MHRA website. For combined review applications these should be completed and submitted on IRAS. A substantial modification may need to be submitted alongside a declaration of early termination where it is necessary to seek an ethics review of related actions such as informing participants and arranging continuing care and follow-up outside the trial.

10.65 The requirement to notify the REC of conclusion or early termination should also apply to all other research with a favourable opinion. In the case of non-CTIMPs, reports should be submitted in the form prescribed by RES and published on the HRA website.

10.66 All notifications of the conclusion or early termination of a study should be acknowledged and reviewed by the Chair or, at the Chair's discretion, by another member of the REC or a Scientific Officer. The REC should be notified in the REC Report. No further action is required unless the Chair considers that issues are raised requiring discussion at a meeting of the REC or sub-committee.

10.67 Once the end of the study has been declared to the REC, it is no longer possible to submit notices of substantial modification. However, it can be helpful to the REC to be made aware of changes affecting key individuals which occur following the completion of a study. For example, CI, PI, trial manager or sponsor contacts may change.

10.68 In very exceptional circumstances, an end of trial may be declared in error and subsequent substantial modifications for the study are sent to the REC. Any such cases should be referred to an Operational Manager.

Transparency Requirements at the end of the study

10.69 Paragraphs 3.19 - 3.23 set out the transparency requirements and expectations for all research including CTIMPs. It also sets out the timeframes for when each activity should be completed. The following transparency requirements are the ones relevant to the end of the study:

a) Publication of results

For CTIMPs, results must be published within 12 months of the end of the study on the public register or registries where the study is registered. This is a legal requirement as per the Clinical Trial Regulations and not doing so would be an offence. For other types of research (except student studies), it is expected that findings, whether positive or negative, are made publicly accessible in a timely manner after the research has finished.

b) Sharing of results

For CTIMPs, the results of the research must be offered to all participants and/or relevant persons in a manner that is understandable to lay people. This is a legal requirement as per the Clinical Trial Regulations. For all other types of research (except student studies), it is expected that results are made available, in a suitable

format and timely manner, to those who took part in it, unless otherwise justified.

c) Sharing data and tissue

Where possible, it is recommended that data and any tissue collected for research are made accessible with appropriate safeguards.

10.70 When sponsors submit a final report they can confirm that results have been published and a summary of results has been offered to relevant persons who wanted to receive them, or what arrangements are in place to do so.

10.71 For CTIMPs, unless an appropriate deferral or waiver is in place, failure to register the study or publish results in the registry (as set out in the Clinical Trial Regulations) will constitute an offence and, if not rectified, may result in action being taken by the MHRA. The HRA will work with the MHRA to support compliance.

Review of a favourable ethics opinion

10.72 The Chief Investigator or sponsor may ask the REC to review its favourable opinion or seek advice from the REC on any ethical issue relating to the study at any time.

10.73 The REC may review its favourable ethical opinion of a study at any time in the light of safety reports, refusal to register the study (if applicable), issues raised by media reports or any other information received about the conduct of the study.

10.74 The REC may also review its favourable ethics opinion of a study in the light of concerns to REC opinions raised by patients, service users, carers, members of the public or patient organisations, researchers etc. where these concerns present relevant new information, not originally considered by the REC, related to any of the following:

a) Social or scientific value; scientific design and conduct of the study.

b) Risks to the safety or physical or mental integrity of participants.

c) The competence or conduct of the sponsor or investigator(s).

d) The feasibility of the study.

e) The adequacy of the location or facilities.

f) Suspension or termination of regulatory approval for the study.

g) Information provided to participants and documentation associated with the study.

10.75 Written representations regarding such concerns should be sent to the Company

Secretary and the Deputy Director of the Approvals Service. The Deputy Director of the Approvals Service or delegated staff will acknowledge receipt of a written concern regarding a REC opinion within 3 working days. Where the concern is related to a REC based in the Devolved Administrations, the notification will be forwarded on for investigation by the equivalent postholders in Scotland, Wales or Northern Ireland

10.76 The Company Secretary and Deputy Director of Approvals Service will consider the concern seeking further information from the correspondent and/or advice from others as necessary to determine whether it meets the criteria in paragraph 10.75 and may be accepted or may be closed. This process should be undertaken within 10 working days.

10.77 Where it is considered that the concern is related to the criteria in paragraph 10.75 and presents relevant new information not originally considered by the REC, then the Deputy Director of Approvals Service will appoint a Complaints Lead to conduct an initial review of the REC decision, seeking advice from others as necessary, to determine:

- compliance of REC review with applicable SOPs;
- whether the REC had clearly and appropriately addressed the information presented in the concern/challenge at the time of their review;
- whether the protocol had been subject to appropriate scientific critique ("peer review").
- whether the nature of the concern or issue raised could attract media or other attention.

10.78 Where the concern does not relate to the categories set out in paragraph 10.75 or is deemed not to present relevant new information it may still be taken forward for determination of compliance with SOPs and/or REC review of the opinion at the discretion of the Deputy Director of Approvals Service, taking advice from others as necessary.

10.79 Depending on the outcome of the initial review of the REC opinion the Complaints Lead in liaison with the Deputy Director of Approvals Service may:

- close the matter and issue a formal response, where the REC review was fully compliant with SOPs and appropriately and fully addressed the concern
- liaise with the REC Chair to respond to the concerns raised;

- require the REC to review its opinion in the light of the new information presented.

10.80 Where it is decided that the REC should review its opinion based on the new information presented, the study should normally be allocated to the next full meeting of the REC. A senior member of the Operations team and/or the Complaints Lead should also attend the meeting. Depending upon timing it may be necessary to convene an additional meeting of the REC.

10.81 Where the REC is required to review its opinion the Complaints Lead, shall inform the person raising the concern of this and the associated timescale for re-review. The Company Secretary will issue the formal acknowledgement to the complainant and will also keep the complainant informed of any extensions to the timeline for review.

10.82 The Complaints Lead should submit the outcome of the REC review to the Company Secretary and Deputy Director of the Approvals Service. The formal response to the individual who raised the concern will be issued by the Company Secretary. The Complaints Lead may also need to issue a separate communication from the REC to the Chief Investigator and Sponsor in order to notify them of the outcome and any further follow up required.

10.83 Where, following the formal notification of the outcome of the initial review and/or subsequent REC review of the concern to the individual or body raising the concern continues to formally challenge the REC opinion (or revised opinion following REC review); then such further formal challenges should, where they have not been sent directly, be forwarded to the appointing authority lead for consideration.

10.84 Where necessary, the appointing authority lead, or delegated staff, will contact the challenger(s) asking them to provide a letter setting out the reasons for the challenge in detail. Unless and until such a letter is provided the challenge will not be considered.

10.85 Upon receipt of a letter setting out the reasons for the challenge in detail the Appointing Authority Lead, or delegated staff, will acknowledge receipt of the challenge within 3 working days.

10.86 The appointing authority lead will consider the points raised, seeking advice from others as necessary, to determine whether the challenge should be accepted or may be closed. The appointing authority lead should send a copy of the challenge to the REC Chair and the Deputy Director of Approvals Service advising them of the next steps to be taken.

10.87 Following initial consideration of the challenge the appointing authority lead may:

- close the matter and issue a formal response, where satisfied that the REC review was fully compliant with SOPs and appropriately and fully addressed the concern or the REC review of its original opinion had appropriately and fully addressed the original concern and/or subsequent challenge(s); or
- refer the challenge(s) to the Deputy Director of Approvals Service, for further review/advice to include a review of the decision to close the original concern. In doing so, the appointing authority lead should request a written report from the Director of Approvals Service (who will consult with the relevant REC Chair(s)). The Deputy Director of Approvals Service and the Chair must provide the report within 4 weeks.
- Take other action as considered necessary.

10.88 The appointing authority lead (in England this is the Head of Approvals Support and Improvement) should inform the challenger/s of the review procedures to be undertaken and the expected decision timescale.

10.89 Where the challenge is referred to a nominated individual or body for advice, the following may be considered:

- compliance of REC review with SOPs;
- whether the REC had clearly and appropriately addressed the information presented in the concern/challenge at the time of their review including whether the REC had provided justification for any changes to aspects of the application which they were originally concerned or satisfied with;
- (if applicable) whether the REC's review of its original ethics opinion has now considered all relevant information including that presented by the concern/challenge;
- whether advice from a second REC or others may be required.

10.90 The challenge and the report from the Deputy Director of Approvals Service should be considered by the nominated individual or body within 4 weeks of receiving the report.

10.91 Any decision on the challenge taken by the appointing authority lead following referral to for advice (including any subsequent advice given by a second REC) will be considered to be final and binding. No further challenge related to that REC opinion will be considered unless this presents further relevant new information in accordance with paragraph 10.78.

10.92 If the appointing authority was minded to issue a decision which contradicted the advice, this decision would need to be supported by the Appointing Authority Board in England, Scotland and Northern Ireland and the Welsh Government in Wales.

RES Suspension or termination of opinion on a non-CTIMP

10.93 A favourable ethics opinion on a non-CTIMP may be suspended or terminated by the REC due to serious concern about the ethical acceptability of the study relating to one or more of the following:

(a) The scientific validity of the study.

(b) Risks to the safety or physical or mental integrity of participants.

(c) The competence or conduct of the sponsor or investigator(s).

(d) The feasibility of the study.

(e) The adequacy of the location or facilities.

(f) Suspension or termination of regulatory approval for the study.

10.94 In the case of multi-location studies, the favourable ethics opinion for a particular location may be suspended or terminated by the REC following new information received about the suitability of the location. The favourable opinion could continue to apply to other trial locations in these circumstances.

10.95 Before suspending or terminating an opinion, the REC should consider whether it is appropriate to first notify the sponsor of the action it intends to take, setting out its concerns in full and giving the sponsor opportunity to address them within a specified timeframe, by issuing a Notice of Intention to Suspend or Terminate a Favourable Opinion (NISTFO). However, immediate suspension is permitted where the REC judges there would be a serious risk to the health or safety of participants if the study continued in present circumstances.

10.96 Immediate termination of the opinion without prior notice or suspension is permitted only where regulatory approval for a study has also been terminated.

10.97 A REC should not terminate an opinion while relevant investigations by other bodies are still ongoing, unless regulatory approval has also been terminated. An opinion may be suspended pending the outcome of investigations.

10.98 Where concerns raised in a NISTFO are satisfactorily addressed by the sponsor, the REC should send a further letter confirming that the favourable opinion remains in

place.

10.99 All actions relating to possible suspension or termination of an opinion should be discussed either at a full meeting or in sub-committee. Where immediate action is required, either to issue a NISTFO or to suspend an opinion to protect participants from a risk of harm, this may be authorised by a sub-committee involving the Chair and at least two other members. The action should be reviewed and ratified at the next full meeting of the REC.

10.100 The Deputy Director of Approvals Service, or relevant individuals of the Appointing Authority in Wales, Scotland or Northern Ireland, should be informed prior to issuing a NISTFO or a letter of suspension or termination.

10.101 A decision to terminate an opinion should always be taken at a quorate meeting of the full committee.

10.102 When suspending or terminating an opinion, the REC should weigh carefully the implications for any research participants already recruited and consider whether any advice or direction should be given to the sponsor, for example on informing participants or arranging for continuing treatment outside the study.

10.103 The sponsor should be notified of a decision to suspend or terminate by the Chair using SL42A. The letter should specify the following:

- whether the opinion is suspended or terminated,
- the reasons for the suspension or termination,
- the date from which the suspension or termination applies,
- the sponsor's right to appeal to the REC,
- any advice or direction in relation to participants already recruited;

and, in the case of suspension:

- the period of the suspension and arrangements for further review,
- any conditions which are to be satisfied before the favourable opinion may be re-confirmed, either generally or at a particular location.

10.104 A copy of the letter should be sent to the Chief Investigator and the sponsor. In the case of a multi-location study, it is the responsibility of the sponsor to ensure that other investigators, local collaborators and care organisations are informed.

10.105 An opinion should normally be suspended for no longer than 6 months. The suspension should be kept under regular review at each full meeting of the REC,

taking account of any further information received from the sponsor or other bodies. Once the sponsor has satisfied the conditions attached to the suspension, the favourable opinion should be re-instated. If the conditions have not been satisfied within 6 months, the REC may consider terminating the opinion. However, exceptionally the suspension may be extended if the outcome of relevant investigations are still awaited. During a period of suspension, the sponsor may make representations in writing at any time if it considers that there are no reasonable grounds for the suspension.

10.106 A sponsor may appeal against a decision to terminate an opinion. Notice of intention to appeal should be submitted in writing within 90 calendar days. The appeal should be considered at the next full meeting of the REC. The sponsor should be given the opportunity to attend and make further representations.

Review of opinion on a CTIMP

10.107 Procedures for review of opinion on CTIMPs are set out in paragraphs 14.22 - 14.25.

Further reporting after the conclusion of the trial

10.108 If after the conclusion or early termination of a CTIMP or other clinical research, the risk/benefit analysis is considered to have changed, the sponsor or Chief Investigator should notify the REC in case this affects the planned follow-up of trial participants. The plan for further action to inform or protect participants should be described.

Final reports

10.109 For all project-based research (i.e. not research tissue banks or research databases) that have received a favourable ethics opinion from a REC a final report on the research should be submitted to the Research Ethics Service within one year of the conclusion of the research. In the case of early termination, provision of a final report is at the discretion of the sponsor.

10.110 The final report is an opportunity for the sponsors to inform the REC of how they have complied with transparency requirements. For CTIMPs, these requirements are set by the Clinical Trial Regulations.

10.111 All final reports will be acknowledged within 30 calendar days. The REC should be notified of the receipt of the report in the REC Report. The REC can ask to see a copy of the final report on request.

Transfer of REC responsibility

10.112 The responsibilities of a REC for an ongoing study (or research tissue bank or database) may be transferred to another REC in the following circumstances:

(i) The REC ceases to operate.

In this case the Head of Approvals Support and Improvement should make arrangements for all the business of the REC to be taken over by a successor REC or RECs. For CTIMP studies, approval must be gained from UKECA for the transfer.

(ii) Two or more RECs are merged to form a new REC.

In this case all the business of these RECs will normally be taken over by the newly formed REC, provided it has the necessary legal recognition(s). Any business for which it is not legally recognised should be transferred to other appropriately recognised REC(s).

(iii) The REC no longer has legal recognition for a particular type of study.

The Head of Approvals Support and Improvement should transfer REC responsibility for these studies to other appropriately recognised REC(s).

(iv) The REC requests that responsibility for a study is transferred to another REC.

This applies only to non-CTIMPs. A REC may make such a request where for example a significant conflict of interest has arisen during the study (e.g. the CI joins the REC as a member), or the REC considers it no longer has crucial expertise required to maintain effective ethical oversight of the study following changes in membership or that it lacks expertise to give an opinion on significant changes proposed in a substantial modification (e.g. to include participants lacking capacity). Such requests should be considered by the Head of Approvals Support and Improvement. If supported, the study should be transferred to another appropriate REC with the agreement of its Chair and given a new REC reference number. The sponsor and CI should be notified.

Back to Contents

Section 11: Research databases

General policy

11.1 Organisations responsible for the management of research databases anywhere in the UK may apply for ethics review of their arrangements for collection, storage and use of data, including arrangements for release of non-identifiable data for analysis by external researchers.

11.2 A favourable ethics opinion is required under the REC Policy Document for specific research projects involving the collection of personal information from past or present users of health or social care services, or use of previously collected information from which individual users of these services could be identified, either directly from that information or from its combination with other information in, or likely to come into, the possession of someone to whom the information is made available.

11.3 However, there is no requirement for research databases to apply for ethics review under the UK Policy Framework for Health and Social Care Research.

11.4 REC review is only required by law where the activities of a research database would include accessing or otherwise processing the identifiable data of patients or services users in England and Wales outside the normal care team without consent. This would require an application to both the Confidentiality Advisory Group and a Research Ethics Committee under Section 251 of the NHS Act 2006 to set aside the common law duty of confidentiality owed by care professionals to their patients or service users (for detailed guidance on such applications, see paragraphs 14.58 onwards.

11.5 Applications for ethics review of research databases will therefore normally be made on a voluntary basis. The benefit of applying for an ethics review of a research database is to facilitate programmes of research without a need to submit several project-based applications.

Defining a research database

11.6 The following paragraphs define s a research database for the purpose of ethics review. The term “research database” may be used in other research contexts where application for ethics review as a research database is not relevant.

11.7 A “research database” means:

> “A structured collection of individual-level personal information, which is stored for potential research purposes beyond the life of a specific research

project with defined endpoints."

11.8 "Research purposes" in this context refers to analysis of data to answer research questions in multiple projects.

11.9 Databases not created originally for research purposes may be used subsequently for research purposes. Also, databases originally established for a single research project can subsequently be used for additional research purposes. Research databases may therefore include:

- Databases originally established for research purposes, including those:
    - Originally supporting one or more specific research projects but now used for other research purposes.
    - Intended to establish a baseline for further research generating and directly supporting future research studies.
    - Designed to support meta-analysis through collation of other databases.
- Databases established for purposes other than research, where there is now an intention to use that database for research purposes, for example databases originally established to support:
    - Delivery of care.
    - Audit or service evaluation.
    - Population or health care planning.
- Databases established for multiple purposes, such as disease registers, where research is one of the intended purposes.

11.10 Personal information may include data from images, as well as the images themselves.

11.11 Biological samples alone, although latent "stores" of potential information about the individuals who provide them, are not treated as information per se. However, effective use of biological samples in research typically involves collection of data about the donor. Samples of disease tissues are normally held with information about diagnosis, and for maximum usefulness the dataset may include more detailed information about demographics, medical history, clinical treatment and outcomes. This data may be made available to researchers alongside samples for analysis. For the purposes of ethics review data provided with biological samples is considered to be part of a "research tissue bank" (RTB). Application for ethics review should be

made under the RTB process and the ethics issues relating to the data considered as part of an over-arching review of the research resource (see Section 12).

11.12 The research database application review process is not intended to apply to any of the following:

- Databases containing only aggregated rather than individual-level information;
- Databases holding contact information only, e.g. of participants in a specific project or potential participants who may be approached to take part in future research;
- Databases established to support one specific project only, e.g. a clinical trial database, or a registry established by a pharmaceutical company or device manufacturer for post-market surveillance of patients treated using a particular medicinal product or device;
- Databases holding information about research studies, e.g. clinical trial registers, or databases established by research regulators or governance bodies to support their functions;
- Databases held with biological samples as part of a research tissue bank.

Applications for ethics review of research databases

11.13 Applications for ethics review of a research database should be prepared using the specific form for this purpose in IRAS. The application should be made by the person with overall responsibility for the management of the database, who will be regarded as the data controller. The application should be supported by a data custodian, who will be a senior person within the organisation responsible for the database, other than the applicant, who is independent of the research database team and able to provide assurance that appropriate information governance is in place.

11.14 Standard procedures for booking and submission apply to research databases (see Section 1).

11.15 It is recommended that applicants apply to a flagged REC for review of research databases (see paragraph 1.7 - 1.16).

Validation

11.16 Research database applications should be regarded as valid if all the following criteria are satisfied:

i. The research database application form has been correctly completed in IRAS and all supporting documents have been submitted (the checklist

in IRAS indicates which documents are mandatory).

ii. All relevant sections and questions in the application form have been completed

iii. The application form has been electronically authorised by the applicant (the data controller) and by the data custodian.

iv. A short curriculum vitae (a maximum of two pages is recommended) has been submitted for the applicant.

v. A protocol or other document describing arrangements for management of the database has been submitted. This should be a comprehensive outline of the purpose, operation, methods, policies and governance of the database.

vi. Where consent is to be sought from participants, copies of all information sheets and consent forms have been submitted.

vii. All supporting documents have been marked with version numbers and dates.

viii. Where an unfavourable opinion has been given to a previous application related to the same research database, the additional criteria in paragraph 1.42 apply.

ix. For renewals of the REC favourable opinion for an existing research database, a covering letter should be provided which lists all projects for which data has been released in the previous five years. The list should give the full title of each project, the name of the chief investigator, the sponsor, the location of the research, and the date of approval by the establishment (see paragraph 11.32)

11.17 RECs will normally only review databases established by organisations within the UK. However, project specific applications related to the provision of data from UK participants to non-UK databases may be accepted for review where the database plans to collect data relating to UK participants.

Process of ethics review

11.18 The process of ethics review is the same as for project-based applications. All references to the Chief Investigator in Sections 2 and 3 of the SOPs should be read as applying to the person submitting the application.

11.18. Where an unfavourable opinion is issued, the usual options for further ethics review

described in Section 8 of SOPs apply.

11.19. Substantial modifications to the terms of the favourable ethics opinion for a database should be reviewed under the procedures in Section 6 of SOPs in the same way as substantial modifications to specific research projects. The substantial modification should be submitted via IRAS.

Summary of issues for ethics review

11.20 RECs undertaking ethics review of research databases should note the following guidance on issues to be considered in applications. An ethics review form for research databases is available in the reviewer portal and published on the HRA website.

- Purpose and value of the database; why is the resource needed, how will it add value to existing sources of data in the field?
- Arrangements for management and oversight of the database.
- Expertise available within the research database team.
- Types of data to be collected; what personal identifiers or particularly sensitive information will be held?
- Access to identifiable data within the research database team and confidentiality policies.
- Database security policy.
- Arrangements for data collection and consent from data subjects; information sheets and consent forms; policy on withdrawal of consent.
- Engagement with patients, services users and public, policy on publication of research findings.
- Types of research to be supported by the database.
- Applications from external researchers, how decisions on access are made.
- Processes for effective de-identification of data extracts prior to release.
- Conditions of data sharing agreements with external researchers, in particular no attempt to re-identify data subjects through linkage with other databases and no onward disclosure to third parties.

Scope of the favourable ethics opinion

Approval for the research database team

11.21 Where a favourable opinion is given, this will give ethics approval to the research database team to collect, store, and use identifiable data for the purposes for which consent has been sought. These should be described in the REC application and will typically include activities such as data cleansing, linkage, anonymisation / pseudonymisation, audit and verification, as well as analysis in research studies conducted by researchers within the team. The research database team will normally have consent from individuals to process their personal data, unless exceptionally approval from the HRA on the advice of the CAG is also obtained to process identifiable data without consent (see paragraph 11.4 and Section 14). The research database must have policies in place to ensure the continued security of the data, to minimise access to identifiable data within the research database team and ensure that duties of confidentiality are enforced. The REC should expect to receive suitable assurances about these policies in the application.

Generic approval for external researchers

11.22 Applicants may also seek generic approval on behalf of external researchers receiving non-identifiable data from the research database to undertake specific research projects, without the need for applying for a separate ethics review each time. Data sharing is encouraged in the interests of maximising the research potential of stored data, provided that adequate safeguards are in place to protect confidentiality. The REC may give generic approval extending to studies undertaken by external researcher's subject to conditions (see paragraph 11.26). Where generic ethics approval has not been granted for the research database, a separate ethics review for any individual research projects' conducted using the data would need to be applied for.

11.23 In this context, "external researchers" means researchers outside of the research database team. They may be within the wider organisation (e.g. in another department of the organisation responsible for the database) or in other organisations.

11.24 External researchers will generally not have consent to process personal data unless they are established collaborations and have been specifically covered in the terms of consent (in this case, they may be considered part of the research database team). Therefore, external researchers relying on generic ethics approval must not receive data in identifiable form or be able to identify individuals through linkage with other databases. Where an external researcher requires access to identifiable data or

further contact with data subjects to undertake a study, a project-specific application should be made for ethics review.

11.25 The research database team must have clear policies in place for making decisions on access and processes for effectively de-identifying data extracts prior to release. Data sharing agreements should be in place with researchers.

Conditions of ethics approval

11.26 Where ethics approval is given, the REC should issue a set of approval conditions appropriate to research databases, normally including the following:

(a) Approval is given for a period of five years, which may be renewed on consideration of a fresh application. (see paragraphs 11.33 on renewals and 12.49 - 12.50)

(b) Data from the database may only be processed to support research within the fields of health or social care research described in the application form.

(c) Research has been subject to scientific critique, is appropriately designed in relation to its objectives and is likely to add something useful to existing knowledge.

(d) The processing of data will comply with the terms of informed consent from data subjects (where applicable).

(e) Where generic approval is given for external researchers, the following additional conditions apply to the release of data:

- Research must be conducted in circumstances such that data subjects are not identifiable to external researchers. Datasets must be effectively de-identified prior to release (i.e. anonymised or pseudonymised);
- Researchers must undertake to treat datasets in confidence and not to attempt re-identification of data subjects through linkage with other data;
- Data sharing agreements must be in place with researchers to ensure processing of data in accordance with the terms of the ethics approval and any other conditions required by the research database team.

(f) The data controller should maintain a record of all internal and external

research projects using data from the database. The record should contain at least the full title of the project, a brief summary of its purpose and the dataset released (including any sensitive data), the name of the chief investigator, the sponsor, the location of the research, the date on which the project was approved by the research database team, whether the data was accessed in identifiable form, and any relevant reference numbers. The REC may request access to this record at any time.

(g) The research database team should maintain a publicly accessible register of research projects using data from the database.

(h) Substantial modifications should be notified to the REC using IRAS. The following should always be notified as substantial modifications:

- Any significant change to the policy for use of the data in research, including changes to the types of research to be undertaken or supported by the database;
- Any significant change to the types of data to be collected and stored, or the circumstances of collection;
- Any significant change to informed consent arrangements, including new/modified information sheets and consent forms;
- Any proposed change to the conditions of ethics approval;
- Appointment of a new data controller;
- Any other significant change to the location, management or governance of the database.

(i) The REC should also be notified for information of any change in the contact details for the data controller, or where the role of Data Custodian passes to another senior person at the establishment.

(j) The REC should be notified as soon as possible of any breach of the approval conditions, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the resource.

(k) Plans to close the database should be notified to the REC as early as possible and at least two months before closure. The REC should be informed what arrangements are to be made for destruction of the data or transfer to a database managed by another organisation. Where data is

transferred, the favourable ethics opinion is not transferable.

11.27 The REC has the discretion to modify these conditions or to attach other approval conditions as appropriate to the application.

11.28. The favourable ethics opinion is given for a period of up to five years and will be renewable (see paragraphs 11.32 - 11.35).

11.28 The ethics review applies to the management of the database, including arrangements made with collaborators. There is no requirement for specific ethics approval for Data Collection Centres (DCCs) who provide data under the terms of a supply agreement between their organisation and the database. DCCs are not regarded as research locations for the purpose of the UK Policy Framework for Health and Social Care Research. However, local collaborators at Data Collection Centres within the NHS/HSC will require internal permission from their NHS/HSC care organisation to collect and supply data relating to NHS patients.

NHS management permission

11.29 Research permission is not required by collaborators at DCCs as these are not regarded as research locations.

11.30 The research database team is advised to provide NHS R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available.

11.31 NHS researchers undertaking specific research projects using data supplied by a database require permission from R&D offices at all organisations where the research is actually conducted, whether or not the database has ethics approval. Where the data is received in non-identifiable form and the research is covered by the terms of generic ethics approval for the database, no further REC application is required.

Renewal of the favourable ethics opinion

11.32 The favourable ethics opinion for research databases is given for five years initially but may be renewed for further periods of five years at a time. The presumption is that the favourable ethics opinion will continue to be renewed provided that the REC has adequate assurances of the continuing value of the resource and compliance with the terms and conditions of approval. (Refer to paragraph 12.49 - 12.50 on late renewals)

11.33 Procedures for renewal at the five-year point are as follows:

(a) A reminder should be issued about the need to submit the renewal application six months prior to the due date. All documentation in respect of the renewal of approval will be managed under a new IRAS ID. Applicants only need to submit the versions of documents that are still in use e.g. if participants are no longer being recruited, a participant information sheet does not need to be submitted.

(b) The data controller should submit an updated version of the original application form and supporting documentation taking into account any changes during the intervening period.

(c) The research database renewal application and supporting documents should be submitted to the next available meeting of the REC which originally issued the favourable opinion (or another REC appointed to manage ongoing business if the original REC is no longer in operation);

(d) The application to renew the favourable ethics opinion should include a covering letter which lists all projects for which data has been released in the previous five years. The list should give the full title of each project, the name of the chief investigator, the sponsor, the location of the research and the date of approval by the establishment.

The renewal documentation should be reviewed at the next available full meeting of the REC. The Data Controller should be invited to attend. The REC may issue one written request for further information following the meeting;

(f) Assuming the REC is content to renew the approval, a new REC favourable opinion letter for the research database should be issued.

(g) Pending issue of the renewal letter, the previous favourable ethics opinion will remain in place;

(h) Renewed approvals will normally be for a further period of five years, (see section 12.49 - 12.50 on renewals)

Exceptionally, the REC may decide not to renew the approval where it has serious concern about one of the following:

- Failure to use the resource to support research of public benefit
- Failure to comply with the conditions of the REC favourable opinion

11.34 Before deciding not to renew the favourable ethics opinion, the REC should first write

to the data controller by issuing a provisional opinion and allowing opportunity for further representations to be made.

11.35 When reviewing the renewal, if an error or poor practice related to the original ethics review is identified, the REC should raise these issues when reviewing the renewal. No action would need to be taken retrospectively however, the renewal should be an opportunity to ensure that the researchers take the appropriate corrective action. This should be managed by requesting further information as part of a provisional opinion rather than issuing an immediate unfavourable opinion.

Back to Contents

Section 12: Research involving human tissue

Statutory provisions

12.1 Detailed guidance on the provisions of the Human Tissue Act 2004 relating to research involving human tissue is at Annex E. The Human Tissue Act ("HT Act") applies only in England, Wales and Northern Ireland, except for provisions relating to DNA and the storage of relevant material for transplantation, which are UK-wide.

12.2 Under the Human Tissue (Scotland) Act 2006, the statutory provisions relating to research apply only to research involving tissue and organs from the deceased. A summary of these provisions is at Annex E. The Scottish Government has established an independent non-statutory accreditation scheme that applies standards for the collection and provision of tissue and organs from NHS patients by Scottish Health Boards for use in research issued. Accreditation is required for facilities (hereafter termed NHS Scotland biorepositories) working within Scottish Health Boards that are collecting and storing tissues from NHS Scotland patients and are providing access to retained tissue for future research. NHS Scotland biorepositories can also provide oversight of local research tissue banks to ensure that accreditation standards are applied. Accreditation is not required when a Scottish Health Board is only involved in the collection and storage of tissues for use in specific NHS REC approved projects and when the surplus tissue is subsequently destroyed in an appropriate manner or transferred to an accredited NHS Scotland biorepository following completion of the project. Accreditation is subject to a positive opinion on the activities given by a Scottish REC. Given the requirement for a positive opinion from a Scottish REC for accreditation and the role of NHS Scotland biorepositories in oversight of local research tissue banks, Scottish RECs should assess research tissue bank applications in Scotland. REC applications for research tissue banks in Scotland should be accompanied by a letter of support from the relevant NHS Scotland biorepository and the REC should inform the relevant NHS Scotland biorepository of the outcome of the assessment. However, where a Scottish REC is considering an application for research involving human tissue from England, Wales or Northern Ireland, the full procedures set out in this section will apply.

General policy

12.3 The general policy is that the REC review process should:

- Provide an ethics review of research using human tissue collected, stored and used within the UK as required by legislation and the REC Policy Document.
- Undertake the ethics review in a proportionate way, taking account of any material risk of harm or distress to donors, their families, and other research participants.
- Facilitate valuable research using human tissue of benefit to society, within the legal framework established by statute and common law within each country of the UK.

Requirements for ethics review of research involving human tissue

England, Wales and Northern Ireland

12.4 Under the HT Act and the HT Regulations, researchers in England, Wales and Northern Ireland will legally require ethics approval in order to carry out the following activities:

- Storing or using the tissue of living or deceased persons for a research project on premises without a licence from the Human Tissue Authority (HTA) (see paragraphs 26-28 of Annex E).
- Storing or using tissue from the living for a research project without consent where the samples are anonymised to the researcher, i.e. in circumstances where the researcher is unable to identify the tissue donor and not likely to be able to do so in future (see paragraph 9(ii) of Annex E).
- Analysing human DNA in cellular material (or using the results of DNA analysis) without consent, in circumstances where they are unable to identify the tissue donor and not likely to be able to do so in future (see paragraphs 16-18 of Annex E).
- Storing or using tissue for a research project where consent is required and the tissue is from adults unable to consent for themselves (see paragraphs 18-20 of Annex E).
- Exporting tissue which is taken from the living and there is no consent in place for future use in research.

12.5 The HT Regulations provide that, where an ethics review is required for research involving tissue in England, Wales or Northern Ireland, it must be given by:

- Any committee established or recognised under the Clinical Trials Regulations (including recognised RECs in Scotland), or

- Any other committee or persons appointed to advise on the ethics of research on human tissue and recognised for that purpose by or on behalf of the Secretary of State, National Assembly for Wales or the Department of Health, Department of Health in Northern Ireland. For health-related research this means any REC which is part of the UK Health Departments' Research Ethics Service under the REC Policy Document.

12.6 These provisions mean that, in general, researchers requiring ethics approval for the purpose of the HT Act will need to apply to a recognised REC under the Clinical Trials Regulations or to a REC established under the REC Policy Document. RECs should accept any valid application requiring ethics approval under the Act.

Scotland

12.7 Under the Human Tissue (Scotland) Act 2006, research must be approved in writing where it takes place on an organ retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal. Approval is also required for new research on organs retained from a post-mortem examination that took place before 1 September 2006. An Order made by Scottish Ministers under the Act specifies that such approvals must be given by:

- Any ethics committee established or recognised under the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, or;
- Any other committee established to advise on the ethics of research investigations in human beings and recognised for that purpose by or on behalf of the Secretary of State or the Scottish Ministers. This includes all RECs established under the REC Policy Document. However, operationally, it would be beneficial for an application to be considered by a Scottish REC with knowledge of the requirements of Scottish accreditation scheme (section 12.2).

12.8 The Human Tissue (Scotland) Act 2006 does not require ethics approval where the research involves tissue blocks and slides retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal, or tissues and organs retained from a hospital post-mortem examination, and there is authorisation for its use in research. However, under guidance issued on the Act in Scotland those responsible for the research project would be expected to obtain REC approval. In addition to this, the General Policy set out in section 12.3 also applies in Scotland with respect to tissue from the living.

Ethics and compliance with the law

12.9 When reviewing research involving human tissue, the role of the REC is to give ethics approval rather than to apply the law. The REC's opinion should be informed by and take account of legal requirements but is not limited by them. Where difficult issues of legal interpretation arise, it is not the role of the REC to provide legal advice. RECs may provide researchers with essential information about the legal requirements. However, researchers should seek their own legal advice and/or consult the HTA for advice where appropriate.

12.10 In some cases, consent to the storage and use of tissue in research is not legally required by the HT Act, in particular for existing holdings and, subject to ethics approval, tissue from living persons not identifiable to the researcher. However, this does not mean that all such tissue should be used freely and without regard to issues of consent or other ethical considerations. For tissue collections in Scotland, RECs should consider the requirements of the accreditation scheme for NHS Scotland biorepositories (section 12.2).

Applications for ethics approval

12.11 There are two possible routes to obtaining ethics approval for research involving storage or use of human tissue or analysis of DNA:

(i) Application for approval of a specific research project Such approval lasts only for the duration of the project as described in the protocol and the application form. Should any delay occur in completing the project, it is acceptable to extend its duration to undertake the procedures described in the protocol (see paragraph 10.9).

(ii) Application for approval of a research tissue bank (RTB), which may provide generic ethics approval prospectively for a range of research to be carried out by the establishment responsible for the bank and/or by other researchers to whom tissue is released by the bank within the conditions of the ethics approval. Such approval may be given for a period of up to five years and will be renewable (see paragraphs 12.34 onwards for renewals and 12.49 onwards for late renewals). A storage licence will be required from the HTA for tissue banks storing relevant material in England, Wales or Northern Ireland. In Scotland, NHS Scotland biorepositories need to be accredited through the independent accreditation scheme established by the Scottish Government (see

paragraph 12.2).

Project-based applications

12.12 Project-based applications should be made in the following cases:

(a) CTIMPs involving storage or use of human tissue.

(b) Research involving removal of human tissue or other bodily material from the living as part of the protocol (i.e. primarily for research purposes).

(c) Research involving the use of stored tissue or data in circumstances where the researcher is able, or could be able, to identify the donor(s).

(d) Research involving any contact with donors or relatives to seek consent, obtain further data or undertake any other research procedure.

(e) Research involving use of stored tissue from a research tissue bank which does not have ethics approval from a REC.

(f) Research involving use of stored tissue from a research tissue bank, which has ethics approval from a REC, but the terms of the approval do not extend to generic approval for projects receiving tissue from the bank (see paragraph 12.30(c)), or the tissue bank manager requires the researcher to obtain project-specific approval before agreeing to release tissue.

(g) Research involving stored tissue from a clinical diagnostic archive that is not licensed to store tissue for use in research and does not have ethics approval.

(h) Research in Scotland involving organs, tissue blocks and slides no longer required for Procurator Fiscal purposes following post-mortem examinations, or research involving organs and tissue retained from hospital post-mortem examinations.

(i) Research involving analysis of human DNA extracted from acellular material.

12.13 Project-based applications should be made in accordance with normal booking procedures (see section 1). The application should be allocated as follows:

- CTIMPs should be allocated to recognised committees in accordance with normal procedures (see section 1).

- Non-CTIMPs seeking ethics approval for the purposes of the HT Act should normally be allocated for review by a REC in England, Wales or Northern Ireland. However, they could be reviewed by a recognised REC in Scotland and this might be appropriate where for example the research is being conducted in (or involves tissue from) both Scotland and another part of the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to Scotland A REC.
- Other non-CTIMPs taking place anywhere in the UK and submitted for ethics review under departmental policy or on a voluntary basis, but not seeking ethics approval for the purposes of the HT Act, may generally be allocated to any REC in the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to a designated REC in Scotland (Scotland A REC).
- In Scotland, non-CTIMPs seeking ethics approval for the purposes of the Human Tissue (Scotland) Act 2004 and associated guidance should normally be allocated to a Scottish REC but may be allocated to a REC in England, Wales, or Northern Ireland if necessary (see paragraph 12.7).

12.14 "Donors" includes any living person whose tissue is to be stored or used for the purpose of the research, even if the research requires no contact with them.

12.15 Applications should be reviewed in accordance with normal procedures. Standard policy on approval conditions applies to the review (see paragraphs 3.16 - 3.27).

12.16 Ethical approval for project-specific applications is confined to the specific project described in the protocol and the application form. It is permitted to seek approval for a project to be undertaken in several stages provided that these are clearly defined in the protocol and relate to the same set of research questions. It is not acceptable to use the project-specific application form to seek open-ended approval for use of stored tissue in future research programmes (although the terms of the consent itself may be generic and open-ended, allowing for future approved research using the same samples). Applications not relating to specific projects with a study protocol may be invalidated. It is not acceptable to submit substantial modifications to approved projects in order to use tissue for another project with a different set of research questions.

12.17 Where a researcher in England, Wales or Northern Ireland makes a specific project-based application but also plans to store the tissue beyond the life of the project for use in further projects, the following options are available:

- At the end of the project, the researcher may make a further project-based application. The application must be submitted no later than the date on which the first project ends (as defined in the protocol), otherwise continued storage of the tissue would require a licence from the HTA. If the second application is also granted approval, continued storage of the tissue for use in this project will be lawful without a licence. At the end of the second project the options set out in this paragraph apply in the same way.
- At the end of the project the researcher may make an application for review of a RTB, including details of the plans for further research. The RTB will also require a storage licence from the HTA.
- Applications may be made simultaneously at the outset for review of the project and the longer term RTB, using both application forms. The two forms should be submitted to the same REC and reviewed in conjunction. A storage licence will be required from the HTA at the end of the initial project.
- If none of the above steps are taken, the researcher will need to arrange for disposal of the tissue or transfer to an appropriately licensed tissue bank or apply to the HTA for a licence.
- The researcher may retain the tissue without a HTA licence under the original approval provided it is being held as a record of the completed research project, for example, to verify and quality check the research data. If additional time is needed to undertake the main analysis, then the REC should be informed of this before the end of study is declared. Storage without a licence for verification and quality checking should be for no longer than 12 months after the end of study has been reached and should be in accordance with the length of time set out in the protocol. If the tissue continues to be stored without a licence for the purpose of any other research project, further approval should be sought before the approval (including the additional time after the declaration of the end of study, if applicable) for the existing project expires.
- Where a researcher in Scotland makes a specific project-based application but also plans to store tissue collected from NHS Scotland patients beyond the life of the project for use in further projects, the options for this should be discussed with an accredited NHS Research Scotland biorepository where applicable.

12.18 If an application form states that tissue samples will be obtained from a UK based licensed Research Tissue Bank, there is no requirement for applicants to specify the

name(s) of the Research Tissue Banks on the application form. The project can be ethically approved without confirmation of which Research Tissue Bank the samples will be collected from as this information may not be known at the time of the submission.

Applications for ethics review of research tissue banks

12.19 Organisations responsible for the management of research tissue banks (RTB) anywhere in the UK may apply for ethics review of their arrangements for collection, storage, use and distribution of tissue. A "research tissue bank" (or "biobank") is defined for the purpose of these SOPs as:

> 'A collection of human tissue or other biological material, which is stored for potential research use beyond the life of a specific project with ethics approval or for which ethics approval is pending.'

12.20 Tissue banks storing human tissue for use in as yet unspecified research must obtain a licence from the HTA (except in Scotland where there is an accreditation scheme for NHS Research Scotland biorepositories). There is no requirement for tissue banks to obtain ethics approval under the HTA or the REC Policy Document. Research tissue bank applications will therefore be made on a voluntary basis, however, ethics approval for a bank may have benefits by facilitating programmes of research without a need to seek ethics approval foreach individual research projects.

12.21 RECs will normally only review RTBs established by organisations within the UK. However, applications related to non-UK RTBs may be accepted for review where the bank plans to collect tissue or data relating to UK participants. Where this is the case a project specific application should be submitted for the collection of tissue or data from participants in the UK.

Application form for RTB

12.22 An applicant seeking review of a RTB should select the relevant option in the IRAS project filter. This will produce a customised version of the form suited to review of tissue banking arrangements rather than a specific research project.

Booking, allocation and validation of RTB applications

12.23 New applications and renewals should be allocated to one of the flagged RECs

12.24 RTB applications should meet the following validation criteria:

(a) The RTB application form has been correctly completed in IRAS and submitted to the REC together with all supporting documents (the

checklist in IRAS indicates which documents are mandatory);

(b) All relevant sections and questions in the application form have been completed;

(c) The application form has been electronically authorised by the applicant and, where applicable, by the Designated Individual;

(d) A short curriculum vitae (a maximum of two pages is recommended) have been submitted for the applicant;

(e) Where consent is to be sought from new donors, or further consent is to be sought from previous donors, copies of all information sheets and consent forms have been enclosed;

(f) All supporting documents have been marked with version numbers and dates;

(g) Where a RTB, which will be storing or collecting relevant material, in England, Wales or Northern Ireland has already obtained a licence from the HTA, a copy of the licence should be provided (it is not mandatory to have obtained the licence before applying for ethics review). In Scotland, the REC should inform the applicable accredited NHS Research Scotland biorepository about the application, which may need to be accompanied by a letter of support from the biorepository;

(h) Where an unfavourable opinion has been given to a previous application related to the same RTB, the additional criteria in paragraph 1.42 apply.

(i) For renewals of the REC favourable opinion, a covering letter should be provided which lists all projects for which tissue has been released in the previous five years. The list should give the full title of each project, the name of the chief investigator, the sponsor, the location of the research and the date of approval by the establishment. (see paragraphs 12.34 onwards for renewals and 12.49 onwards for late renewals)

12.25 The ethics review applies to the management of the tissue bank, including arrangements made with collaborators. There is no requirement to apply for ethics approval for individual research locations or centres involved in the collection, storage or use of tissue. However, local collaborators at Tissue Collection Centres within the NHS will normally require management permission from the NHS care organisation in order to collect tissue or data from NHS patients and supply it to the tissue bank.

Process of ethics review for RTB applications

12.26 The process of ethics review will generally be the same as for project-based applications. All references to the “Chief Investigator” in Sections 2 and 3 of the SOPs should be read as applying to the person submitting the application.

12.27 Where an unfavourable opinion is issued, the usual options for further review described in Section 8 will apply.

12.28 Substantial modifications to the terms of the ethics approval for a RTB (see paragraph (f)12.30(f)) should be reviewed under the procedures in Section 6 in the same way as substantial modifications for specific research projects.

General guidance on ethics review of RTBs

12.29 RECs undertaking the ethics review of RTBs should note the following general guidance. An ethics review form for research tissue banks is available in the reviewer portal and published on the HRA website.

The review should focus particularly on the following ethics issues:

- arrangements for the collection of new samples;
- requirements to seek consent from new donors, further consent from previous donors, or consent from relatives where the donors are deceased;
- the terms of informed consent as set out in information sheets and consent forms;
- justification for storage and use of tissue for research without specific consent where not legally required;
- the policy for provision of tissue to researchers, including arrangements for ensuring adequate scientific critique of projects and the conditions under which samples will be released;
- any plans to provide donors with feedback of any clinically significant information obtained in research using their samples.

- Ethics review should be proportionate, balancing the need to protect the safety, rights and wellbeing of donors with the need to facilitate research of value to society.
- In England, Wales and Northern Ireland the ethics review should generally complement the process of licensing by the HTA rather than duplicate it. Similarly,

in Scotland in relation to the Scottish accreditation scheme. RECs are not required to address governance issues that will be covered in detail in the licensing process. These include the suitability of the Designated Individual and other persons named on the licence, premises, facilities and equipment for storage of samples, donor identification and tracking systems, records of consent, security and risk management, arrangements for the disposal of samples, quality systems, internal/external audit, staff training. Although there is an ethical dimension to some of these issues, it is primarily the responsibility of the HTA to set standards and ensure compliance (in Scotland standards are assessed by the Scottish accreditation scheme for NHS Scotland biorepositories.

Approval conditions for RTBs

12.30 The REC should issue a set of approval conditions appropriate to RTBs, which should normally include the following:

(a) Approval is given initially for a period of five years, which may be renewed

(b) Except in Scotland or for RTBs not holding any relevant material, a copy of the licence from the HTA should be provided when available (if not already submitted). The REC should be notified if the HTA renews the licence, modifies the licensing conditions or revokes the licence, or of any change of Designated Individual. In Scotland, the REC should inform the applicable accredited NHS Research Scotland biorepository about the application, which may need to include a letter of support from the biorepository

(c) Where the applicant has applied for generic ethics approval for projects receiving tissue - without further project-specific applications being required - the following conditions apply to the release of tissue:

- Tissue may only be released for research within the fields of research described in the application form.
- The RTB should have management arrangements in place to be satisfied that the research has been subject to scientific critique, is appropriately designed in relation to its objectives and is likely to add something useful to existing knowledge.
- Where samples have been donated with informed consent for use in future research (“generic consent”), the RTB should be satisfied that the use of the samples complies with the terms of donor consent.
- All samples and any associated clinical information must be non- identifiable

to the researcher at the point of release (i.e. anonymised or linked anonymised).

- Samples will not be released to any project requiring further data or tissue from donors, or any other contact with donors except under ethically approved arrangements for the feedback of clinically significant information to patients.
- A supply agreement must be in place with the researcher to ensure storage, use and disposal of the samples in accordance with the terms of the ethics approval and any other conditions required by the RTB.

(d) It is not mandatory for RTBs to apply for generic ethics approval on behalf of end users. A RTB may opt to require all researchers receiving tissue to apply individually to a REC for ethics approval using the project-based application form. Where generic ethics approval is sought, it is open to the REC either to give simple ethics approval to the research tissue bank only or to give an approval which includes generic approval for end users.

(e) The applicant should maintain a record of all research projects for which tissue has been released. The record should contain at least the full title of the project, a brief summary of its purpose, the name of the Chief Investigator, the date on which the project was approved by the RTB and details of the tissue released. The REC may request access to this record at any time.

(f) Substantial modifications (see paragraph 12.28) should be notified to the REC using IRAS. The following should always be notified:

- Any significant change to the policy for use of the tissue in research, including changes to the types of research to be undertaken or supported by the RTB;
- Any significant change to the types of biological material to be collected and stored, or the circumstances of collection;
- Any significant change to informed consent arrangements, including new/modified information sheets and consent forms;
- Request for approval to release tissue to researchers (if not sought as part of the initial application), or changes to the terms of the approval;
- Appointment of a new tissue bank manager (i.e. the person making the application and responsible for further reporting to the REC);

- Any other significant change to the governance of the RTB.

(g) To request generic ethics approval for projects to which tissue is supplied, the RTB should submit a new application rather than a modification.

(h) The REC should be notified for information of any change in the contact details for the applicant or appointment of a new Designated Individual at the establishment.

(i) The REC should be notified as soon as possible of any breach of the approval conditions, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the tissue (such incidents would also need to be reported immediately to the HTA).

(j) Plans to close the RTB should be notified to the REC (and to the HTA) as early as possible and at least two months before closure. The REC should be informed what arrangements are to be made for disposal of the tissue or transfer to another RTB. Where tissue is transferred to another RTB, the ethics approval is not transferable.

12.31 The REC has the discretion to modify these conditions or to attach other approval conditions as appropriate to the application. Research conducted using tissue provided by a RTB under the conditions in paragraph 12.30(c) will be considered to have ethics approval from the REC under the terms of the ethics approval for the RTB. In England, Wales and Northern Ireland this means that the end user researcher will not require a licence from the HTA for storage of the tissue for use in relation to that research project.

Renewal of approval

12.32 Ethics approval for RTBs is given for five years initially but may be renewed for further periods of five years at a time. The presumption is that approvals will continue to be renewed provided that the REC has adequate assurances of the continuing value of the resource and compliance with the terms and conditions of approval. (see paragraph 12.49 on late renewals)

12.33 Procedures for renewal at the five-year point are as follows:

(a) A reminder should be issued about the need to submit the renewal documentation six months prior to the due date - all documentation in respect of the renewal of approval will be managed under a new IRAS project ID. Applicants only need to submit the versions of documents that are still in use e.g. if participants are no longer being recruited, a participant information sheet does not need to be submitted.

(b) The RTB manager should submit an updated version of the original application form and supporting documentation taking into account changes during the intervening period. The renewal application should be submitted to the original REC (or another REC appointed to manage ongoing business if the original REC is no longer in operation)

(c) The application to renew the approval should include a covering letter which lists all projects for which tissue has been released in the previous five years. The list should give the full title of each project, the name of the chief investigator, the sponsor, the location of the research and the date of approval by the tissue bank.

(d) If the renewal documentation is not received by the due date, the process in section 12.49 should be followed

(e) The renewal documentation should be reviewed at the next available full meeting of the REC. The RTB manager should be invited to attend (The REC may issue one written request for further information following the meeting.

(f) Assuming the REC is content to renew the approval, a new REC favourable opinion letter should be issued. Pending issue of the renewal letter, the previous ethics approval will usually remain in place; (refer to paragraph 12.49 on late renewals)

(g) Renewed approvals will normally be for a further period of five years, backdated to the end of the previous five year period.

12.34 Exceptionally, the REC may decide not to renew the approval where it has serious concern about one of the following:

- Failure to use the resource to support research of public benefit.
- Failure to comply with the terms and conditions of approval.

12.35 Before deciding not to review the ethics approval, the REC should first write to the RTB manager setting out its concerns and allowing opportunity for further representations to be made.

12.36 When reviewing the renewal, if an error or poor practice is identified related to the original ethics review, the REC should raise these issues when reviewing the renewal. No action would need to be taken retrospectively however, the renewal should be an opportunity to ensure that the researchers take the appropriate corrective action. This should be managed by requesting further information from the

applicant rather than issuing an immediate unfavourable opinion

Project applications relating to tissue held by an approved RTB

12.37 Where a researcher applies for review of a specific project involving tissue held by an approved RTB, the IRAS project ID for the RTB should be cited in the application. It is recommended that the application should be submitted to the REC which reviewed the RTB. Where for any reason the application is made to a different REC (for example, because an agenda slot is not available at the tissue bank REC), the REC reviewing the application may consult with the tissue bank REC and request sight of relevant documentation.

Import and export of human tissue

12.38 The HT Act makes provisions relating to the import and export of human tissue for research purposes. In legal terms this includes the import of tissue from Scotland for storage for use in research in England, Wales or Northern Ireland; and the export to Scotland for research purposes of tissue from the living or the deceased in England, Wales or Northern Ireland.

12.39 The HTA has issued a Code of Practice setting standards and providing guidance on the import and export of human bodies, body parts and tissue. The import or export of tissue is not a licensable activity. However, once it is imported the storage of tissue for use in research is licensable unless the research has received approval. The consent provisions of the HT Act do not apply to tissue that has been imported.

General policy on ethics review of research outside the UK

12.40 It is not the role of the REC in the UK to review research conducted outside the UK. The same policy generally applies to review of research-related activities conducted outside the UK in support of UK research, for example arrangements for removal or storage of tissue from overseas donors and for taking informed consent where appropriate. RECs are not required to give an ethics opinion on activities carried out outside the UK. It is more appropriate that the activities are subject to ethics review in the country concerned, considering its own legal requirements, ethical guidelines, culture and the language used in the consent process. Equally, it is important that research-related activities conducted in the UK in support of overseas research are ethically reviewed in the UK where they involve tissue from the living or the deceased in the UK.

12.41 The following paragraphs give guidance on applications involving import or export of tissue to or from the UK. (For the purposes of these SOPs, human tissue research or

research-related activities undertaken in Scotland are considered to be UK research.)

Applications relating to import of tissue (Including from Scotland to England, Wales & Northern Ireland)

12.42 Under the Regulations made under the HT Act, researchers undertaking projects using imported tissue require ethics approval from a REC where the material will be held on unlicensed premises in England, Wales or Northern Ireland during the project. Where a researcher requires ethics approval for legal reasons, the REC should accept the application for review. Otherwise, RECs are not required to review applications outside their normal remit under the REC Policy Document and relating solely to the storage or use of imported tissue for research. Where an application involves imported tissue, the REC should seek justification for importation in preference to sourcing material within the UK where practicable. The REC may also seek confirmation that consent for research has been or will be given by donors in the source country. (The requirement for consent to use existing or surplus samples will be a matter of ethical judgement, depending on the age of the samples, whether identifying information about the donors is held, and whether consent would be required in equivalent circumstances in the UK.). However, RECs are not expected to undertake detailed review of the consent arrangements or any other research activities undertaken by collaborators in the source country.

Applications relating to export of tissue

12.43 RECs should accept for review applications involving the collection of tissue from the living or the deceased in the UK for export for use in research outside the UK. The REC must limit its opinion to the activities to be conducted within the UK. In particular, the REC should consider issues relating to informed consent.

Standard letters and approval conditions

12.44 When reviewing applications involving import or export of tissue, standard letters may be amended at the discretion of the REC to clarify the terms of the opinion. Standard approval conditions may also be modified.

Renewal of RTB & RD applications

12.45 Staff will be alerted to research tissue bank and research database applications coming up for renewal via the Application alerts tab in HARP. A reminder to renew the favourable ethics opinion for the RTB and RD will appear in HARP six months prior to the due date. Staff should issue the reminder letter to prompt the applicant to

submit the application to renew the ethics opinion however, it is the responsibility of the applicant to ensure that the application to renew the ethics opinion is submitted within the required timeframe.

12.46 If the application to renew the favourable ethics opinion will be delayed beyond the due date, the applicant must inform the REC of the reasons for the delay in advance of the date from which the favourable ethics opinion for the RTB or RD lapses.

12.47 There are sometimes cases of applications to renew the favourable ethics opinion being delayed due to extenuating circumstances such as illness, and where this is the case **and the reason has been provided to the REC in advance of the due date**, the Approvals Specialist/ REC Manager in liaison with the REC Chair can consider on a case-by-case basis whether the duration of the existing favourable opinion can be extended and liaise with the applicant to agree a new date on which the renewal application will be submitted.

12.48 If the renewal application is delayed and a reason for the delay was not provided and an extension was not agreed by the REC in advance of the deadline, the Approvals Specialist/REC Manager should notify the breaches team and inform the applicant that the failure to renew the favourable ethics opinion has been recorded as a breach. For RTBs in England, Wales and Northern Ireland, the Human Tissue Authority's licensing team will also be notified of the breach. For RTBs based in Scotland, the nodal NHS Scotland-accredited Biorepository which provides the RTB with governance oversight will be notified.

12.49 For research tissue banks and research databases with generic ethics approval, if the renewal is delayed and an extension has not been agreed with the REC in advance of the due date, any ongoing project specific studies which were being conducted under the governance of the RTB or RD during the five year period are considered to still have a favourable ethics opinion however, this would not apply to any new studies applying to the tissue bank/database after the five year period ended (unless an extension had been agreed).

12.50 If an application to renew the REC favourable opinion will not be submitted but the research database or research tissue bank will remain open, the documentation should not state that the resource has a REC favourable opinion.

Back to Contents

Section 13: Research involving adults unable to consent for themselves

Introduction

13.1 This section of SOPs sets out the procedures governing ethics review of research involving adults unable to consent for themselves. It deals separately with:

- Clinical trials of investigational medicinal products (CTIMPs), for which UK-wide statutory provision is made by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 as amended ("Clinical Trials Regulations").
- Non-CTIMPs, where the legal position differs across the UK with important implications for the process of ethics review.

A. Clinical trials of investigational medicinal products (CTIMPs)

13.2 The inclusion in CTIMPs of adults unable to consent for themselves is governed by the provisions of the Clinical Trials Regulations. Adults lacking mental capacity to consent may be recruited into CTIMPs where the following apply:

- there are grounds to expect that the participant will gain benefit from the IMP which outweighs any anticipated risks
- the trial is essential to validate data obtained in other clinical trials involving persons able to give consent, or by other research methods
- the trial relates directly to a life threatening or debilitating condition from which the participant suffers

New applications

13.3 Applicants for CTIMPs should indicate on the IRAS project filter if they plan to include adults unable to consent for themselves, and complete the additional set of questions generated. An adult is defined in the Clinical Trials Regulations as a person aged 16 or over.

13.4 When answering the questions at booking, the applicant should declare that the trial involves adults unable to consent for themselves in order that the application is allocated to an appropriate REC.

13.5 CTIMPS involving adults who lack capacity/adults with incapacity must be reviewed by a recognised REC. **However, the REC does not also need to be**

flagged to review studies involving adults lacking capacity/adults with incapacity.

(Note: Phase 1 trials cannot include adults unable to consent for themselves, as one of the requirements of the Clinical Trial Regulations is that there are grounds for expecting that administering the investigational medicinal product will produce a benefit to the participant. This is incompatible with the definition of a Phase 1 trial under the Regulations.)

13.6 Where the trial is to be conducted at one or more locations 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.

Ethics review

13.7 The REC undertaking the review of a trial involving adults unable to consent for themselves is required to consider whether the research is justified having regard to the conditions and principles specified in the Clinical Trials Regulations. These include provisions for informed consent to be given by the participant's legal representative. A definition of "legal representative" for this purpose is given in the Clinical Trial Regulations.

13.8 The ethics review of a CTIMP involving adults with incapacity in Scotland is governed by the provisions of the Clinical Trials Regulations and the Adults with Incapacity Legislation.

B. Research other than CTIMPs

Mental Capacity Act 2005 (England and Wales) and the Mental Capacity Act (Northern Ireland) 2016

Scope

13.9 The provisions of sections 30-33 of the Mental Capacity Act 2005 (England and Wales) came into force on 1 October 2007. Any new research starting on or after 1 October 2007 in England and Wales must comply fully with the provisions of sections 30-33 if it is "intrusive research" involving one or more adults unable to consent for themselves.

13.10 The provisions of Part 8 of the Mental Capacity Act (Northern Ireland) 2016 came into operation on 1 October 2019 through the Mental Capacity (Research)

Regulations (Northern Ireland) 2019. Any research in Northern Ireland involving adults lacking capacity to consent for themselves must comply fully with the provisions of Part 8.

13.11 Sections 30-34 of the Mental Capacity Act 2005 (England and Wales and Part 8 of the Mental Capacity Act (Northern Ireland) 2016 make detailed provision relating to research involving living adults aged 16 or over who are unable to consent for themselves. The provisions of these Acts do not apply to CTIMPs nor to research involving the deceased. Although there are separate Acts governing inclusion of Adults Lacking Capacity in England/Wales and Northern Ireland, there is sufficient parity such that a REC in England, Wales or Northern Ireland may provide ethics review as 'appropriate bodies' under both these Acts.

13.12 The Human Tissue Acts govern the post-mortem removal, storage and use of organs and tissue.

13.13 The application of these provisions is not limited to medical and biomedical research, health-related research or research taking place within the NHS. It may apply to research in the context of social care and in any other context where participants could lack capacity to give informed consent.

Intrusive research

13.14 For the purposes of sections 30-33 of the Mental Capacity Act 2005 (England and Wales, and Part 8 –Research of the Mental Capacity Act (Northern Ireland) 2016, "intrusive research" is defined as:

> "… research that would be unlawful if carried out on or in relation to a person who had capacity to consent to it, but without his consent".

This definition means that some research undertaken in relation to people who lack capacity does not require approval under sections 30-33, because consent is not a legal requirement. Research would not be intrusive where it is limited to one or more of the following:

(i) Processing within the usual care team of identifiable data previously obtained in the course of health or social care and now used for secondary research purposes; (Note: However, where it is known at the time data is collected that there is an intention to use it for research purposes, consent should be sought, and this would be 'intrusive'.)

(ii) Processing of non-identifiable data outside the usual care team;

(iii) Processing of identifiable data outside the usual care team, where the research has (or will have) Section 251 support (not applicable to Northern Ireland) In Scotland the equivalent data will require to have Caldicott Guardian approval if held within a single Health Board or Public Benefit and Privacy Panel (PBPP) approval for data covering a number of Health Board areas or data held by Public Health Scotland.

(iv) Storage or use of human tissue or other biological material in circumstances where consent is not required under the Human Tissue Act 2004 (see Annex E), in particular where the material is:

- not 'relevant material' (e.g. plasma, serum);
- relevant material from the living which is not identifiable to the researcher and REC approval will be obtained; or
- relevant material which is an 'existing holding' already stored prior to 1 September 2006.

Requirements for approval by an appropriate body

13.15 There are two types of approval for research under the Acts:

- Approval under section 30 (Mental Capacity Act 2005 (England and Wales) and under Section 132 (Mental Capacity Act (Northern Ireland) 2016) to undertake any "intrusive research" where the participants include one or more adults unable to consent for themselves.

13.16 Approval under the Acts must be given by an "appropriate body". Under the Mental Capacity Act 2005 (Appropriate Body (England) Regulations 2006 and equivalent Regulations made by the National Assembly for Wales (NAW) (referred to collectively in these SOPs as the "Appropriate Body Regulations"), the appropriate body is a committee:

(a) established to advise on, or on matters which include, the ethics of intrusive research in relation to people who lack capacity to consent to it, and

(b) recognised for that purpose by the Secretary of State or Welsh Ministers (to whom the functions of the NAW have now transferred by virtue of the Government of Wales Act 2006).

13.17 In Northern Ireland, approval must be given by an “appropriate body” under the Mental Capacity Act (Northern Ireland) 2016 made by the Northern Ireland Assembly. The ‘appropriate body’ is a person, other body or committee:

(a) which approves research involving persons who are over 16 and lack capacity in relation to participation in the research, and

(b) Specified for that purpose by the Department of Health under Paragraph 132 (4) of the Mental Capacity Act (Northern Ireland) 2016 enacted as the Mental Capacity (Research) (Amendment) Regulations (Northern Ireland) 2022.

Reference paragraph 13.11 for parity arrangements between England/Wales and Northern Ireland Mental Capacity Acts.

13.18 All NHS RECs established under the REC Policy Document in England and Wales, and the Social Care REC, are recognised for this purpose both by the Secretary of State for Health and Welsh Ministers and are therefore appropriate bodies for the purposes of approving research under the Mental Capacity 2005 (England and Wales) Act. The Ministry of Defence RECs are also recognised for research within their remits. All named NHS and HSC RECs in England, Wales and Northern Ireland are recognised as appropriate bodies under Paragraph 132 (4) of the Mental Capacity Act (Northern Ireland) 2016 enacted as the Mental Capacity (Research) Amendment Regulations (Northern Ireland) 2020.

13.19 An approval by an appropriate body in England and Wales applies to the conduct of the research in England, Wales, and Northern Ireland.

Flagged RECs

13.20 Although legally any REC established under the REC Policy Document in England/ Wales and Northern Ireland may approve research under the MCAs, a panel of flagged RECs for research involving adults unable to consent for themselves has been established. (For general guidance on flagged RECs, refer to paragraphs 1.7-1.11).

13.21 The panel includes a REC in Scotland for the purposes of research taking place in Scotland (for guidance on research taking place in more than one UK country, see paragraph 13.37).

New applications for section 30 approval ((the Mental Capacity Act (2005) England and Wales) and/ or Section 132 approval the Mental Capacity Act (Northern Ireland) 2016

13.22 The applicant should indicate on the IRAS project filter if they plan to undertake intrusive research involving adults unable to consent for themselves at any stage of the project (including following loss of capacity) and complete the additional set of questions generated. For the purposes of the Mental Capacity Acts, an adult is a person aged 16 or over.

13.23 When booking to a REC, the applicant should declare that the study plans to include adults unable to consent for themselves.

13.24 The application should be booked to a REC which is flagged for review of research involving adults unable to consent for themselves. Research taking place in England or Wales only should be allocated to a flagged REC in England or Wales respectively but may, if necessary, be allocated to a flagged REC in the other country. Research taking place in both countries may be allocated to any flagged REC in England, Wales or Northern Ireland.

13.25 For procedures relating to research to be conducted in Scotland or Northern Ireland as well as in England and/or Wales, see the guidance in paragraph 13.37.

13.26 The application should be registered on HARP as an application for Mental Capacity Acts approval and use the modified standard letters generated.

13.27 It should be noted that there could be cases where Mental Capacity Acts approval is sought but not given on the basis that the research could be carried out equally effectively if confined to participants able to consent for themselves. In these

circumstances, a favourable opinion could be given without approval under the Mental Capacity Acts. The REC would need to be satisfied that appropriate changes had been made to the inclusion criteria and recruitment procedures.

13.28 The Chief Investigator may either appeal or submit a further application under the procedures in Section 8. Any appeal or new application will be allocated to a flagged REC.

Sources of guidance on the Mental Capacity Act 2005 (England and Wales)

13.29 The Mental Capacity Act Code of Practice is published at: https://www.gov.uk/government/publications/mental-capacity-act-code-of-practice

Under section 42(4) of the Act, researchers are legally required to have regard to the Code of Practice. RECs should also have regard to the Code of Practice when considering any type of application under the Act, and in particular to the following chapters:

- Chapter 2, setting out the underlying principles of the Act.
- Chapter 3, on helping people make decisions for themselves.
- Chapter 4, dealing with the assessment of capacity.
- Chapter 11, describing the criteria for approval of research.

13.30 The Secretary of State and the Welsh Ministers have published guidance under section 32(3) of the Act on arrangements for nominating consultees where no willing personal consultee (e.g. a family member or other unpaid carer) can be identified. Researchers are required to have regard to the guidance.

Adults with Incapacity (Scotland) Act 2000

13.31 The inclusion of participants unable to consent for themselves in research other than CTIMPs taking place in Scotland is governed by the Adults with Incapacity (Scotland) Act 2000 (“AWI Act”).

13.32 Under the AWI Act, the research must be approved by “the Ethics Committee” constituted by Scottish Ministers under Regulations made under the Act. All such

applications should be allocated to the designated REC in Scotland, which will review the application under section 51 of the AWI Act.

13.33 The guidance relating to expert advice in paragraph 13.27 does not apply. The constitution of the designated REC in Scotland is determined by Regulations made under the AWI Act.

13.34 For procedures relating to research to be conducted in other UK countries as well as Scotland, see the guidance in paragraph 13.37.

Northern Ireland (Mental Capacity Act (Northern Ireland) 2016)

13.35 The inclusion of participants unable to consent for themselves in research other than CTIMPs taking place in Northern Ireland is governed by the Mental Capacity Act (Northern Ireland) 2016, which came into operation on 1st October 2019, through the Mental Capacity (Research) Regulations (Northern Ireland) 2019.

Guidance is available in the MCA (NI 2016) Money & Valuables and Research Code of Practice – August 2019, Chapter 3.

13.36 For procedures relating to research to be conducted in other UK countries as well as Northern Ireland, see the guidance in paragraph 13.37.

Research other than CTIMPs: research conducted in different UK countries

13.37 The table below summarises application procedures for non-CTIMPs to be conducted in different UK countries. In particular, it gives guidance on applications conducted under more than one jurisdiction:

Countries where study locations are	Application process
England and/or Wales only	Apply to any flagged REC in England or Wales.

Scotland only	Apply to a designated REC in Scotland.
Northern Ireland only	Apply to any HSC REC in Northern Ireland.
England/Wales/Northern Ireland and Scotland	Two applications should be made: 1. The England/Wales/Northern Ireland application should be made to a flagged REC in England or Wales or Northern Ireland. 2. The Scotland application should be made to a designated REC in Scotland. Separate versions of the application form in IRAS should be submitted with separate REC reference numbers. Both applications may be submitted at the same time or they may be submitted consecutively; with the first opinion being given in advance of the second application being submitted. The applications will be reviewed separately having regard to the relevant legislation. Any favourable opinion with respect to including ALC will apply only to England/Wales/Northern Ireland or Scotland respectively. Different opinions may be given regarding the inclusion of adults who lack capacity/adults with incapacity. A favourable ethics opinion from either REC means that the study has a favourable ethics opinion to proceed in England/Wales/Northern Ireland **and** Scotland but if the other REC gives an unfavourable opinion, it is not permitted to include adults who lack capacity/adults with incapacity in the country which did not give a favourable ethics opinion. When an application which involves; adults who lack capacity/adults with incapacity, is being undertaken in England/Wales/Northern Ireland and Scotland, the requirement for dual review should be discussed with the applicant. The second REC to undertake the review

	should request the favourable opinion from the first REC by contacting the Approvals staff/REC Manager. The favourable opinion letter should be made available to the REC members of the second REC when reviewing the application. Discussion should be undertaken between the REC Chairs of the two RECs if there is any disparity. Any substantial modifications which do not relate to MCA/AWI need only be submitted to one REC and should not be submitted to both.
England/Wales and Northern Ireland	Apply to any flagged REC in England, Wales or Northern Ireland Only one application is required.

Addition of new locations

13.38 The usual SOPs apply to addition of new locations, except in some situations where the research is extended to a new country for the first time. The following situations should be noted:

- Where research which was previously only taking place in Scotland is extended to England, Wales or Northern Ireland for the first time, a new application should be made to a flagged REC in England, Wales or Northern Ireland.
- Where research is extended to Scotland for the first time, a new application should be made to the designated REC in Scotland.

Substantial modifications to include adults lacking capacity

13.39 Where research is already underway, and it is proposed to include adults unable to consent for themselves for the first time and the research is 'intrusive' (see paragraph 13.14) a substantial modification should be submitted to the REC together with the following:

- Part B Section 6 of the REC application form.
- Revised protocol;
- Information sheets and legal representative or consultee documentation (as appropriate, depending on whether the study is a CTIMP or non-CTIMP and which UK jurisdiction(s) are involved).

13.40 For non CTIMPs, where the original REC is not flagged, and expertise is not available on the committee, advice should be sought from a flagged REC.

13.41 The REC may stop the clock once and request further information in the same way as for a new application. The modification should be reviewed at a full committee meeting.

13.42 For non-CTIMPs being conducted in England, Wales or Northern Ireland the modification should be registered in HARP as an application for section 30 approval under the MCA 2005 (England and Wales) and/or for Section 132 approval under MCA (Northern Ireland) 2016. The opinion letter will include the additional paragraph regarding whether the study was approved under the Mental Capacity Acts.

13.43 For non-CTIMPs being conducted in Scotland, the substantial modification requires review by the designated REC in Scotland under the Adults with Incapacity

(Scotland) Act. The following guidance should be noted:

- If the designated REC in Scotland is not already the REC for the study, it should receive a copy of the original REC application and a full set of study documentation in addition to the documents required under paragraph 13.39.
- If the REC for the study is another REC in Scotland ("first REC"), the substantial modification should be submitted to the designated REC in Scotland rather than the first REC. The designated REC in Scotland will consult the first REC before giving its opinion. If the designated REC in Scotland gives a favourable opinion of the modification, it will take over REC responsibility for the study: all REC documentation should be transferred by the first REC. If it gives an unfavourable opinion, REC responsibility remains with the first REC.
- If the study is being conducted both in Scotland and England/Wales/Northern Ireland, the modification should be submitted for separate review in Scotland and by a REC in England/Wales or Northern Ireland. If the designated REC in Scotland gives a favourable opinion, it will assume REC responsibility for Scotland. Responsibility for the study in England/Wales and Northern Ireland remains with the REC covering those jurisdictions.
- It should be noted that there could be cases where approval is sought but not given on the basis that the research could be carried out equally effectively if confined to participants able to consent for themselves. In these circumstances, a favourable opinion could be given without Section 30 approval under the MCA 2005 (England and Wales) and/or for Section 132 approval under MCA (Northern Ireland) 2016 and under the Adults with Incapacity (Scotland) Act. The REC would need to be satisfied that appropriate changes had been made to the inclusion criteria and recruitment procedures.

Back to Contents

Section 14: Communication with other regulators and review bodies

General policy

14.1 As well as a favourable opinion from a REC, some health and social care research projects require regulatory approvals under a range of legislation applicable to the UK as a whole or to particular countries. Applications for regulatory approval may proceed in parallel with the ethics review. Applicants are encouraged to submit applications at the same time but may apply in sequence if they prefer.

14.2 The Research Ethics Service aims to collaborate closely with regulatory bodies to ensure that the approvals process is robust, efficient, proportionate and facilitative. It aims to:

- Clarify the respective roles and responsibilities of RECs and regulatory bodies both in the review of initial applications and following approval;
- Develop harmonised guidance for researchers in areas of common interest;
- Harmonise as far as possible the information required from applicants by RECs and regulatory bodies within the Integrated Research Application System (IRAS);
- Accept assurances from other regulators in relation to matters within their competence without duplicating their review;
- Share information about the progress of applications, and other information where it may be relevant to post-approval responsibilities;
- Resolve as far as possible any differences of view that emerge during the review process through direct discussion between the REC and the relevant regulator so that consistent advice and direction can be provided to the applicant, while recognising the independent role of each body.

14.3 It is the responsibility of the sponsor to ensure where necessary that a research study has appropriate regulatory approval as well as a favourable ethics opinion before it starts. It is not necessary for evidence of regulatory approval to be provided to the REC before it confirms the final ethics opinion.

14.4 It is the responsibility of the sponsor to ensure that both the REC and the relevant regulator are informed where necessary of significant developments during the initial application process or post-approval. This includes changes made as a result of review by one body that need to be notified to the other body to ensure it has all the relevant information required to give a final decision. Substantial modifications should be submitted during the review process where appropriate (see paragraph 6.8).

14.5 This section of the SOPs sets out detailed procedures for collaboration and communication that have been agreed between the Research Ethics Service and other regulators.

MHRA - Clinical trials of investigational medicinal products

Clinical trial authorisation

14.6 Before commencing a CTIMP, the sponsor(s) is required by the Clinical Trials Regulations to have clinical trial authorisation (CTA) as well as a favourable ethics opinion. An application for CTA should be made to the licensing authority, which is the Medicines and Healthcare products Regulatory Agency (MHRA). A single application should be made using a new part of IRAS, which goes to both the Medicines and Healthcare products Regulatory Agency (MHRA) and a REC at the same time.

The regulatory and ethics reviews are done in parallel and any requests for further information are raised jointly. A single response to these requests leads to a single decision from both reviews.

Roles and responsibilities

14.7 The MHRA has primary responsibility for the safety of medicinal trials. The MHRA Clinical Trials Unit assesses the safety of all proposed CTIMPs, drawing on expertise in pharmacology, toxicology and clinical medicine. The ethics committee may generally rely on the MHRA to assess the safety of medicinal trials, and the MHRA will share their assessment outcome with the REC. The REC is not required to undertake its own expert scientific or safety assessment or seek advice on safety issues from scientific referees. However, the committee should have enough understanding of the scientific background and the safety issues to be able to give an

ethics opinion. In particular, the committee should make an ethics assessment of the information provided in the application about the potential risks and benefits to participants and any measures in place to minimise the risks (e.g. rescue medication, stopping rules, emergency procedures, intensive care facilities). The ethics review must also ensure that the potential risks and benefits of the trial are fully and clearly explained in the participant information sheet.

14.8 The Chief Investigator together with the sponsor is responsible for ensuring that the documentation submitted to the ethics committee fully and accurately describes the safety profile of the IMP and the potential risks to participants. The ethics committee may generally rely on the accuracy of this information.

Communication with MHRA on initial application

14.9 The Clinical Trials Regulations provide for sharing of relevant information on CTIMPs between RECs and the MHRA. Where appropriate, the REC may seek clarification of the status of the CTA application from the MHRA. The REC may also discuss with the MHRA significant concerns about the safety of the trial that have not been resolved by information provided by the applicant.

14.10 Where specific safety issues need to be discussed, or where there is a conflict of views, REC staff should get in touch directly with the MHRA Assessor for the specific trial. Where an Assessor has not been assigned to the trial, REC staff can contact the MHRA Clinical Investigations and Trials (CIT). For general scientific advice, the REC should either seek further information from the sponsor or consult its own referees.

Trials subject to EAG/CHM assessment

14.11 For certain types of trial, the MHRA will seek advice from the Expert Advisory Group on Clinical Trials (EAG) and Commission on Human Medicine (CHM) before giving authorisation. The criteria for trials subject to EAG/CHM assessment are published on the MHRA website. It is possible that the additional advice from EAG/CHM will lead to changes in protocols, with potential implications for ethics review. It is essential that ethics committees are promptly notified of any additional information which is relevant to the ethics application. The primary responsibility for this lies with the sponsor.

Compliance with Good Clinical Practice

14.12 The Clinical Trials Regulations together with internationally recognised guidelines for

Good Clinical Practice (GCP) provide a standard for the conduct of CTIMPs. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical trial participants are protected (consistent with the principles that have their origin in the Declaration of Helsinki), and that clinical trial data are credible and accurate. MHRA GCP inspectors assess compliance with the Regulations and GCP by conducting inspections at the locations of pharmaceutical companies, contract research organisations, non-commercial organisations, investigational trial locations, clinical laboratories, GCP archives and other facilities involved in CTIMPs.

14.13 GCP Inspections are carried out to protect the public (both trial participants and future patients), to meet legal obligations and enforce applicable legislation, to provide assurance of compliance with the Regulations and GCP, to detect and take action relating to serious non-compliance (including fraud and misconduct) and to assist with quality improvements in clinical research. All these activities provide support to the regulatory assessment process on which licence approvals and renewals depend.

Co-operation with GCP inspections

14.14 GCP Inspections do not include assessment of the compliance of RECs with the Regulations or the SOPs. They may however seek to ensure that trials have a favourable opinion from a recognised REC and are being conducted in accordance with the terms of the opinion, this includes complying with the transparency requirements. This may require verification of the application documentation and correspondence held by the REC. Any request from the GCP Inspectorate to inspect documentation will be made in writing to the REC, copied to the Head of Approvals Operations. The REC should normally facilitate the inspection. Any concern on the part of the REC about the inspection should be referred to an Operational Manager. If the matter cannot be resolved locally with the GCP Inspectorate, the Operational Manager should notify the Deputy Director of the Approvals Service, who will instruct the Approvals Operations Manager to contact the GCP Operations Manager at the MHRA.

Notifying MHRA of compliance issues in CTIMPs

14.15 RECs should draw serious concerns about compliance issues in CTIMPs to the under the procedures for notifying possible serious breaches (see paragraph 10.38 - 10.50). In consultation with senior operational management at RES, the HRA will be responsible for deciding whether the information should be shared with the GCP

Inspectorate at the MHRA. Where appropriate, the inspectorate will be notified by email.

14.16 The MHRA should always be notified where one of the following is suspected:

- Conduct of a trial without a CTA or favourable opinion.
- Conduct of the trial at a particular location without a favourable opinion for the location or the Principal Investigator.
- Provision of false or misleading information to the REC in relation to an application for ethics opinion or notification of substantial modification.
- Implementation of a substantial modification without authorisation and/or a favourable opinion as appropriate.
- Failure to notify SUSARs occurring in the trial in the UK in an expedited manner or to provide an Annual Safety Report.
- Failure to notify urgent safety measures.
- Failure to notify the early termination or conclusion of the trial.
- A serious breach of GCP or the protocol.
- Failure to comply with transparency requirements to register and publish results in the registry, as set out in the Clinical Trial Regulations.

14.17 Consideration should also be given to notifying the MHRA where a pattern emerges of repeated minor breaches of GCP or the protocol.

14.18 A recognised REC may notify the MHRA directly of possible non-compliance if it considers it appropriate to do so, although it is recommended that RECs follow the normal reporting procedure through the Quality and Performance Manager. When writing direct to the MHRA, the REC should copy the notification to the Quality and Performance Manager. The Head of Approvals Operations should be kept informed.

14.19 All reports received by MHRA will be acknowledged. Feedback will be provided to the HRA on the findings of any resulting inspections or investigations. RES will arrange for relevant RECs and operational managers to be notified.

14.20 Where the MHRA takes regulatory or enforcement action in relation to the conduct of a CTIMP, the HRA will be notified and a copy of the relevant inspection report provided. RES will arrange for relevant RECs and operational managers to be notified and to receive a copy of the inspection report.

14.21 Copies of inspection reports will not be routinely disclosed to RECs. However:

- Any report on a Phase 1 trial location will be provided to the REC or RECs via the Quality and Performance Manager.
- Reports will be disclosed in any case where regulatory or enforcement action is taken;
- Relevant information from other inspections (or copies of reports where appropriate) may be disclosed on request to the GCP Inspectorate from the REC or by the HRA.

Review of opinion on a CTIMP

14.22 Under the Clinical Trials Regulations, the decision to suspend or terminate the CTA and therefore to halt the trial lies solely with the MHRA. The ethics committee has no power under the Regulations to suspend or terminate the CTA or legally withdraw the ethics opinion given previously. However, the REC may review its opinion in the light of new ethical concerns following any new information received about the trial. It may also notify the MHRA that, if it had received the information with the initial application, its opinion of the trial would not have been favourable. Any such notification should be based on a decision taken at a quorate meeting of the full committee. Preliminary discussion may take place in sub-committee.

14.23 Where appropriate, the Chair should write to the Head of the Clinical Trials Unit by email explaining the Committee's concerns in full. The REC may recommend that consideration is given to suspending or terminating the CTA. Any such recommendation should relate to serious concern about one or more of the following:

a) The scientific validity of the trial.

b) The safety or physical or mental integrity of participants.

c) The competence or conduct of the sponsor or investigator(s).

d) The feasibility of the trial.

e) The adequacy of the location or facilities.

14.24 The CTU will consider what action should be taken in relation to the CTA and will notify the REC accordingly. The action taken could include request to the sponsor for further information, request for modification of the trial, or suspension or termination of the CTA. Further information or clarification may be sought from the REC about its concerns. The CTU may seek separate advice from referees.

14.25 The MHRA will directly inform the REC where it suspends or terminates the CTA (which will automatically halt the trial), and also where it re-instates a CTA following suspension. The REC should consider whether the suspension or termination has any implications for the welfare and safety of patients. The sponsor or Chief Investigator may be requested to provide further information about the steps being taken to inform patients or arrange for their continuing treatment outside the trial protocol. The MHRA should be kept informed of any action taken by the REC.

MHRA - clinical investigations of medical devices

Regulatory requirements for medical devices

14.26 All medical devices coming on to the market are regulated by a series of three Medical Devices Directives covering the safety and marketing of medical devices throughout the European Community. These Directives are transposed into UK law by the Medical Devices Regulations 2002. The Competent Authority for medical devices in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA).

14.27 Under the Directives, no medical device (except for custom-made devices) may be placed on the EU market without UKCA/CE UKNI/CE-marking. For all except the very simplest devices, in order to obtain this marking, the manufacturer must go through a conformity assessment procedure to confirm that the device in question complies with the relevant essential requirements relating to safety and performance.

Clinical investigations of non-UKCA/CE UKNI/CE-marked devices

14.28 In order to demonstrate compliance with the requirements for UKCA/CE UKNI/CE-marking, the manufacturer may be required to generate data from a specifically designed clinical investigation. The objectives of such an investigation are to:

- demonstrate that the device achieves its intended purpose as claimed by the manufacturer;
- determine any undesirable side-effects under normal conditions of use;
- demonstrate that the device does not compromise the clinical condition or safety of the patient or present a risk to the device user.

14.29 The manufacturer must notify any such clinical investigation to the MHRA Devices Division.

14.30 The requirement to notify a clinical investigation to MHRA also applies where a study of a non-UKCA/CE UKNI/CE-marked device is sponsored by a non-commercial organisation such as a university or NHS Trust, but commercialisation of the product is intended. Responsibility for the application to MHRA lies with the company that plans to manufacture and market the product commercially. Notification of MHRA is not required where the device is being developed for use within a single legal entity and commercialisation is not intended. For more detailed guidance, see https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety or the HRA guidance on approval for medical devices research.

14.31 Where notification of a clinical investigation is made, MHRA has 60 calendar days in which to assess the application and inform the applicant of any grounds for objection. Such grounds must be based on issues of public health or public policy. If there are no such grounds, authorisation will be given. The REC should be provided with a copy of the MHRA approval when available, either in the course of the ethics review or following the issue of a favourable opinion.

14.32 Under the Medical Devices Regulations, any clinical investigation of a medical device requiring notification to the MHRA must have a favourable opinion from a REC. Application may be made to any REC within the UK Health Departments' Research Ethics Service, except for the Social Care REC (although an informal listing of 'flagged' RECs has been established – see 1.7). The ethics opinion can be obtained in parallel with the Competent Authority Notification.

Roles and responsibilities

14.33 The MHRA assessors review applications to ensure that enough, appropriate data are available to support the proposed study and that planned safety monitoring and reporting procedures are adequate. This includes ensuring that all necessary pre-clinical testing covering for example design features, materials, sterilisation, electrical testing, toxicology, animal studies, has been carried and the results demonstrate that it is reasonable to proceed to clinical use; and that the investigators are adequately qualified and trained in the use of the device.

14.34 The REC may generally rely on the MHRA to assess issues relating to the safety of the study and the technical specification and performance of the device. It is not required to undertake its own detailed safety or technical assessment. However, it should assure itself that any risks are proportionate to the potential benefits and will be minimised; the risks are clearly described in the participant information sheet; and the instructions for use of the device are clear, accurate and comprehensive,

particularly where the participant is the user.

14.35 The REC is responsible for addressing other ethics issues arising from clinical investigations, such as recruitment, informed consent, confidentiality, indemnity and compensation, incentives and payments, follow-up treatment at the end of the study, suitability of locations, registration or publication of study results. Research involving UKCA/CE UKNI/CE-marked devices

14.36 If a manufacturer conducts a study with a UKCA/CE UKNI/CE-marked device which has been substantially modified or is being used outside its intended purpose, with the intention of generating data to support a change to UKCA/CE UKNI/CE-marking, notification of a clinical investigation to the MHRA is required under the Medical Devices Regulations in the same way as for non-UKCA/CE UKNI/CE-marked devices. The arrangements in paragraphs 14.28 - 14.32 apply.

14.37 Where studies involve UKCA/CE UKNI/CE-marked devices used within their intended purpose without modification, notification of MHRA is not required. Other medical devices research should be submitted for REC review where required under the REC Policy Document.

Communication with MHRA on medical devices research

14.38 Under Article 20 of the Medical Devices Directive (93/42/EC), the Competent Authority is required to treat in confidence any information supplied by the manufacturer in connection with a clinical investigation of a medical device. The MHRA may therefore only provide confidential information to a REC with the express agreement of the manufacturer. The MHRA routinely invites manufacturers, when submitting their initial application, to give their agreement that any information relevant to the safety of the patient or user may be shared with the REC system. Provided such agreement is given, the MHRA will share relevant information with the REC and give advice where appropriate. If agreement is not given, the MHRA must hold all information in confidence. However, where appropriate it may advise the manufacturer to share information with the REC and seek further ethical advice.

14.39 When reviewing a clinical investigation requiring regulatory approval, the REC may seek advice from the MHRA Devices Division if appropriate. Clarification may be sought on issues relating to the safety or performance of the device that may be relevant to the ethics review, for example the description of risk in the participant information sheet. Requests for information should be sent to the Clinical Director of MHRA Devices Division copied to the Regulatory Affairs Manager for Devices with the subject line “URGENT: REC correspondence for Clinical Director”.

14.40 MHRA Devices Division is notified of REC opinions on clinical investigations electronically through access to HARP.

14.41 When reviewing a study of a UKCA/CE UKNI/CE-marked device not requiring regulatory approval, advice from MHRA is not normally required. However, a REC may exceptionally seek advice if it has concerns about the proposed use of the device, for example where it is in a higher risk class (e.g. an implantable device) and there appears to be a lack of supporting data from previous clinical investigations to assure the REC of its safety and performance.

Administration of Radioactive Substances Advisory Committee (ARSAC)

Regulatory requirements

14.42 The administration of radioactive substances in the United Kingdom is governed by the Ionising Radiation (Medical Exposure) Regulations 2017 and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2018 (IR(ME)R). Regulation 5 of IR(ME)R requires that any doctor or dentist (referred to as a 'practitioner') wishing to administer radioactive medicinal products to humans must hold a licence issued by the Secretary of State in England, Health Ministers in Scotland and Wales or the Department of Health in Northern Ireland; their employer must also hold a valid licence. IR(ME)R authorises the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise the Secretary of State, Health Ministers and the Department of Health on the issuing of licences. ARSAC also provides advice on related matters, specifically those associated with radiological safety. The Secretariat to ARSAC is provided by a support unit within Public Health England.

14.43 Where research involves the administration of radioactive substances, additional to those provided as part of routine care, an ARSAC licence must be held at each research location where administrations take place and by each practitioner responsible for administering research exposures. The issue of a licence ("ARSAC licence") is required for any research involving administrations additional to those carried out by the licence holder as part of normal clinical care.

Roles and responsibilities

14.44 ARSAC has primary responsibility for assessing whether the proposed administration of radioactive substances in a research study is appropriate. This includes consideration of:

- whether the administration of radioactive substances is appropriate to the study objectives, taking into account international and UK guidelines;
- the effective or target tissue dose per administration and per participant;
- the risks and benefits to participants from these administrations in combination with other ionising radiation to be administered, considering the age, diagnosis and other characteristics of the research cohort;
- measures to minimise the risks, in particular for women with child-bearing potential;
- alternative investigations involving less or no exposure to ionising radiation;
- the suitability of health professionals and facilities for administration of radioactive substances at each location;
- potential variations in clinical practice between research locations.

14.45 In considering the appropriateness of the administrations and the balance of risks and benefits, both the REC and ARSAC wish to be assured of the scientific validity of the research and its potential benefits for the knowledge of disease and/or the treatment or care of patients. The REC has primary responsibility for reviewing whether the protocol has been subject to appropriate scientific critique (“peer review”) by relevant experts and has been adequately designed to meet its objectives.

14.46 Both the REC and ARSAC wish to be assured that sufficient, comprehensible information is provided to potential research participants about radiation exposures and risks. The REC has primary responsibility for review of the procedures for approaching participants and seeking their consent, including the content of any letters, information sheets and consent forms used for this purpose; and for review of all other ethics issues.

Applications to ARSAC

14.47 Application to ARSAC is a two-stage process, comprising:

- A Preliminary Research Assessment (PRA) form, submitted by the sponsor’s representative
- A new Employer Application Form and new Practitioner Application form can be submitted to obtain licences if these are not already held.

14.48 Sponsors are encouraged to complete the PRA form within IRAS and submit parallel

to the REC application booking with a copy of the Participant Information Sheet (PIS) to allow for early advice to be given by ARSAC to the sponsor on study-wide issues and for the REC to take account of this in the ethics review where appropriate.

14.49 For individual research locations, study sponsors should notify the practitioner (for example, the nuclear medicine physician) and the employer under IR(ME)R about the research protocol during set-up, before any administrations take place at each medical radiological installation. Sponsors will be sent an approval document indicating which procedures have been approved. The Sponsor should provide the approval document to the practitioner and employer.

ARSAC review process and communications with the REC

14.50 The PRA form is normally sent to a research subgroup of ARSAC members for comments. The comments are collated by the Support Unit and a response is sent to the sponsor's representative by email. The aim is to reply within 21 calendar days of receipt of the application. A copy of the response and all subsequent correspondence will be sent to the REC email for information.

14.51 As part of its initial assessment, ARSAC may seek further information from the sponsor and/or make recommendations for changes to the protocol or to relevant sections of the participant information sheet that would need to be made before ARSAC could issue licences for individual locations.

14.52 Licences are not to be copied to the REC office. It is the responsibility of the sponsor and the R&D office at the location to check that a licence is in place before the study starts.

REC review process

14.53 For all applications involving radioactive substances, the Approvals staff/REC Manager should copy the REC's provisional and final opinion letters to the ARSAC Support Unit (arsac@phe.gov.uk) when the application has been reviewed.

14.54 In framing a request for further information, the REC should consider ARSAC's initial assessment of the study (where available). If the assessment is not available at the time of the REC meeting, the REC's request for information may include a requirement for the CI to provide evidence that all issues raised by ARSAC in its initial assessment have been fully addressed. The issue of the REC's final opinion may be deferred until confirmation is provided that ARSAC has no further objection to the study.

14.55 The REC should consider the need to seek advice from the ARSAC Support Unit

before requesting any changes that may have an impact on ARSAC's assessment of the research, in particular changes to:

- Radioactive materials exposures.
- Age range of participants, in particular any extension to include participants under 50.
- Information about radiation exposures and risks in the participant information sheet.

14.56 Where a provisional opinion raises issues relevant to ARSAC's assessment, the ARSAC Support Unit may request sight of the CI's response. Otherwise, it is not necessary for the CI's response to be copied to ARSAC.

14.57 Either body may contact the other at any time to seek their advice, or to request further clarification of the issues considered in their review and the reasons and assumptions underlying their opinion. Either body may review its opinion in the light of further information or discussion with the other body. Any further correspondence with the applicant, and the applicant's responses, will be copied to the other body.

Confidentiality Advisory Group (CAG)

Statutory requirements

14.58 The Health Service (Control of Patient Information) Regulations 2002 ("Control of Patient Information Regulations") were originally made under Section 60 of the Health and Social Care Act 2001 and continued in force under Section 251 of the National Health Service Act 2006. The Control of Patient Information Regulations apply in England and Wales only.

14.59 Under Regulation 5, confidential patient information may be processed for medical purposes in certain circumstances, provided that the processing has been approved by the Secretary of State for Health. In the case of medical research, the processing must also be approved by a REC. These approvals are referred to as **"Section 251 approval"**.

14.60 Where Section 251 approvals are given, Regulation 4 provides that anything done by a person that is necessary for processing the information is lawful despite any obligation of confidence owed by that person. The approvals therefore have the effect of setting aside the legal duty of confidentiality owed by a health or social care professional in respect of information provided by the patient / service user in the course of their care.

14.61 The Human Fertilisation and Embryology (Disclosure of Information for Research Purposes) Regulations 2010 (“HFE Regulations”) are made under Section 33 of the Human Fertilisation and Embryology Act 1990 (as amended by the Human Fertilisation and Embryology Act 2008). The HFE Regulations apply to the whole of the UK.

14.62 Under the HFE Regulations, certain protected information held on the register of the Human Fertilisation and Embryology Authority (HFEA) may be processed for research purposes subject to authorisation from the HFEA and approval by a REC.

Role of the CAG

14.63 The Confidentiality Advisory Group (CAG) is established under Section 251of the National Health Service Act 2006 (as amended by Section 157 of the Health and Social Care Act 2008). It is an advisory body to the Secretary of State for Health, established to support improvements in information governance practice and to monitor information governance trends in both the NHS and adult social care. The CAG provides leadership and promotes consistent standards for information governance across health and social care.

14.64 CAG provides independent expert advice to the HRA (for research applications) and the Secretary of State for Health (for non-research applications) on whether applications to access patient information without consent should or should not be approved. The role of CAG is to review applications and advise whether there is enough justification to access the requested confidential patient information. Using CAG advice as a basis for their consideration, the HRA or Secretary of State will take the final approval decision.

14.65 The CAG also advises the HFEA on applications for authorisation under the Human Fertilisation and Embryology (Disclosure of Information for Research Purposes) Regulations 2010.

Review responsibilities

14.66 Where applications are made both to the CAG and to a REC, some aspects raise common ethical issues reviewed by both bodies, based on the same dataset in IRAS, and some are reviewed primarily by one or other body.

Common ethical issues

14.67 The CAG and the REC have an equal interest in considering whether disclosure of

identifiable patient information for research without consent is necessary, ethically acceptable and in the public interest.

14.68 In considering the necessity of the disclosure, both bodies wish to be satisfied that the data items are necessary for the research, especially in the case of sensitive data. Applicants are expected to show why it is not reasonably practicable to seek consent or to conduct the research using non-identifiable information; or that there is an overriding justification for undertaking the research without consent.

14.69 In considering the public interest, both the CAG and the REC wish to be assured of the scientific validity of the research and its potential benefits for the knowledge of disease and/or the treatment or care of patients / service users.

14.70 Both bodies consider whether there is an appropriate level of patient / service user involvement in the design, implementation and dissemination of the study. This includes the potential for consulting patient / service user groups on the acceptability of undertaking the research without consent for disclosure of identifiable information.

Issues reviewed by the CAG

14.71 The CAG has the primary responsibility for advising the Secretary of State and researchers on issues of legality relating to the use of patient information and on standards of information governance.

14.72 The CAG reviews the legal aspects of accessing, using, storing and retaining patient identifiable information without consent. This includes consideration of compliance with the Data Protection Act 2018, the Human Rights Act 1998 and the Common Law Duty of Confidentiality.

14.73 The CAG has primary responsibility for issues of data security and confidentiality. It seeks assurance that the research team has adequate arrangements in place to ensure the security of patient identifiable data, through obtaining independent assessment of the security arrangements). It also considers the mechanisms for ensuring that access to identifiable data is limited to those who require it within the research team, and that the data is retained in identifiable form for the minimum period necessary.

14.74 The CAG provides expert advice to researchers on the risk of potential identifiability of individuals in the use of particular datasets and, where appropriate, methods of de-identification and other approaches to reducing risk of identification.

Issues reviewed by the REC

14.75 While both bodies need to be assured of the scientific validity of the research, the REC has primary responsibility for reviewing whether the protocol has been subject to appropriate scientific critique ("peer review") by relevant experts and has been adequately designed to meet its objectives. It is the sponsor's responsibility to arrange such critique, including review of the statistical aspects of the protocol, and to provide the REC with evidence of this.

14.76 Where it is ultimately determined that consent should be sought for disclosure of identifiable information, the REC has primary responsibility for review of the procedures for approaching participants and seeking consent, including the content of any letters, information sheets and consent forms used for this purpose. Where approval is required under the Mental Capacity Act 2005 to include participants unable to consent for themselves, the REC is responsible for ensuring that the criteria under Sections 30-33 of the Act are met, including that reasonable arrangements are in place for consulting carers under Section 32.

Dual review by REC and CAG – standard procedures

14.77 The REC Approvals staff/REC Manager should send a copy of the REC's provisional and final opinion letters to the Confidentiality Advisory Team (CAT) by email. The CAT may request a copy of responses from the applicant to the REC where these could be relevant to the CAG's review.

14.78 The CAT will send a copy of its provisional and final outcome letters, together with the applicant's responses, to the REC email.

14.79 Where the REC gives a favourable opinion, it should include as a condition of its approval a requirement for approval from CAG, before the research can start. The CAG will include a similar condition with its approvals.

14.80 Either body may contact the other directly by email to request further clarification of the issues considered in their review and the reasons and assumptions underlying their opinion.

Resolving differences on key issues

14.81 While both bodies are independent in their decision-making, it is desirable that consistent decisions are reached on common ethical issues, in particular on the necessity of, and public interest in, processing identifiable data without consent and

setting aside the common law duty of confidentiality. Where either review body takes, or expects to take, a different position to the other, direct discussion is strongly encouraged to seek to resolve the differences. The Approvals staff/REC Manager should co-ordinate discussion with the CAT, involving the Chair and lead reviewer(s) as appropriate.

The outcome of any discussions should be recorded.

14.82 Either body may review its opinion in the light of further information or discussion with the other body. Any further correspondence with the applicant will be copied to the other body.

14.83 Where agreement on key issues cannot be reached, the matter should be reported to the Deputy Director of Approvals Service, who will consider what further steps could be taken to facilitate a resolution. Where the application is being reviewed by a REC in Wales and/or the applicant is professionally based in Wales, the Deputy Director of Approvals Service will proceed in consultation with the HCRW Approvals Operations Manager

Procedures following rejection of application by CAG

14.84 Where the CAG rejects an application for section 251 approval or for disclosure of information under the HFE Regulations (or terminates or significantly alters the terms of an approval given previously), the research team may need to amend their protocol, for example by restricting the project to use of non-identifiable data, or by seeking consent from data subjects. Where the project has already received a favourable opinion from the REC, a substantial modification should be submitted. Where the initial application for ethics review is still in process, the changes should be notified to the REC by letter.

Application to the REC only – is an application also required to CAG?

14.85 In this scenario, the applicant indicates in the IRAS Project Filter that the research requires ethics review by a REC but does not require an application to the CAG.

14.86 Where it appears to the REC that the research may require application to the CAG, the REC should seek advice on the matter from the CAT directly by email. The CAT will advise the researcher directly and inform the Approvals staff/REC Manager of the outcome. Where application to the CAG is required, the standard procedures in paragraphs 14.88-14.92 will apply. The REC should make it a condition of a favourable opinion that CAG approval is obtained.

Mental Capacity Act 2005

14.87 Under sections 30-33 of the Mental Capacity Act 2005, approval by an appropriate body ('Section 30 approval', referred to in this section as 'MCA approval') is required to undertake 'intrusive research' involving adults lacking capacity in England and Wales (see Section 13).

14.88 This definition of intrusive research (see paragraph 13.14) means that some research undertaken in relation to people who lack capacity does not require MCA approval, because consent is not a legal requirement. This includes research limited to use of identifiable data with approval from the REC and the CAG under Section 251 or the HFE Regulations. Therefore, there is an inter-relationship between the need for MCA approval from the REC and the need for CAG approval. Where research in England and Wales involves processing of identifiable data from participants who lack capacity outside the care team, it will require one of these approvals but not both (unless it also involves other intrusive procedures). This has implications where one or other application is unsuccessful.

Dual applications in relation to data from patients lacking capacity

14.89 Where the researcher is applying for both REC and CAG approval at the outset, the REC should treat the application as not requiring MCA approval initially (unless it involves other intrusive research procedures in addition to the processing of identifiable data).

14.90 In considering whether it is justified to set aside the common law duty of confidentiality, both CAG and the REC will take account of the principles of the MCA and the scope for complying with the MCA as an alternative to use of section 251. The research team will be expected to have considered:

- The core principles that people should be assumed to have capacity unless it is established that they lack capacity in relation to a particular matter, and that people should be helped to make their own decisions where possible.
- Whether the research would be feasible if restricted to data subjects able to give consent, and the feasibility of seeking such consent.
- Whether it is feasible to undertake the research using non-identifiable data.
- If it is essential to include identifiable data from participants lacking

capacity, whether it would be feasible to seek advice from consultees under section 32 of the MCA as an alternative to section 251 approval.

14.91 The usual procedures relating to communication between the REC and the CAG apply in such cases (see paragraphs 14.88-14.92).

14.92 Where section 251 approval (or approval under the HFE Regulations) is given, MCA approval is then not required (unless the study involves other intrusive research procedures).

Procedures following rejection of application by CAG

14.93 Where the CAG rejects an application and use of anonymised data is not a feasible alternative, the researcher may then need to seek MCA approval. If the project has already received a favourable opinion from the REC, a substantial modification should be submitted with appropriate supporting documentation (see paragraph 13.42). Where the initial application is still in process, the changes to the application and supporting documentation should be submitted to the REC by letter.

14.94 The REC should copy all correspondence relating to the application for MCA approval to the CAG.

Procedures following rejection of MCA application by the REC

14.95 A researcher may apply for MCA approval to process identifiable data from participants lacking capacity, without applying for section 251 approval initially. Where the REC withholds MCA approval, the researcher would then need to explore other ways of undertaking the research lawfully, for example, by using non-identifiable data, or by restricting the research to participants able to consent for themselves. The researcher might, however, seek section 251 approval to set aside the common law duty of confidentiality. This would require an application to the CAG and a substantial modification to the REC. The guidance in paragraphs 14.82 - 14.95 applies to the dual processing of these applications.

Modifications to approved research

Notifying modifications to CAG

14.96 Where research is underway with CAG approval, the applicant is required to notify the CAG of any modifications to the activity set out in the original application. Notification may be made by letter at the time of the modification or as part of the annual review report to CAG if that is due within the next month. The scale and type of modification will determine whether the project can continue under the existing

approval or needs to be re-considered by the CAG.

Modifications to research with dual approval

14.97 Following REC review of a substantial modification, the REC should send to the CAT a copy of the substantial modification together with the opinion letter. There is no need to provide copies of other correspondence or supporting documentation unless requested.

14.98 The CAT will provide the REC a copy of any correspondence from the applicant notifying modifications to the research, together with any further correspondence. Where the CAG has simply noted the modification for information, the CAT will notify the REC accordingly.

14.99 Where either review body takes, or expects to take, a different position to the other on a modification, the guidance in paragraphs 14.81- 14.83 applies.

Substantial modification to study with REC opinion only

14.100 Very exceptionally, a substantial modification to a study with a favourable opinion from a REC only may require section 251 approval for the first time, due to changes proposed to the processing of patient data.

14.101 Where the applicant is in the process of applying to the CAG for section 251 approval in parallel with the substantial modification, the guidance in paragraphs 14.89 - 14.92 applies.

14.102 Where the substantial modification appears to require section 251 approval but the applicant is not planning to apply to the CAG, the guidance in paragraphs 14.96 onwards applies.

Back to Contents

Section 15: Storage and retention of documentation

Statutory requirements

15.1 Schedule 2 to the Clinical Trials Regulations (as amended) requires that the REC retains all the documentation relating to a CTIMP on which it gives an opinion;

- where the trial proceeds, for at least 3 years from the conclusion or early termination of the trial;
- where the trial does not proceed (e.g. it is given an unfavourable opinion, or does not start following a favourable opinion), for at least 3 years from the date of the opinion.

15.2 There is no statutory requirement to retain documentation relating to applications that are withdrawn prior to giving an opinion.

15.3 The Regulations do not exclude retention of documentation for longer than the specified period.

15.4 For the purposes of the Regulations, documentation is considered to be retained where it is held in electronic form and can be accessed where necessary. It is not necessary to retain original paper copies.

General policy

15.5 The provisions of the Clinical Trials Regulations should apply to all specific research studies reviewed by RECs.

15.6 In addition, documentation should be retained on all invalid applications for at least 1 year from the date of invalidation; and for three years where the application is withdrawn by the REC, the CI or the sponsor after the REC review but before a final opinion is given.

15.7 Separate detailed Operational Management Guidance along with the HRA Records Retention Schedule is published relating to the closure of studies, archiving and destruction of application files.

15.8 Signed final copies of the minutes of full REC meetings and sub-committee business, where relevant, should be retained electronically for at least 20 years and then transferred to the place of deposit, as per the records management policy in the relevant Nation. Draft versions of the minutes should be uploaded to HARP and may be deleted once the final version has been ratified and signed.

.

15.9 Electronic records of studies will be retained indefinitely.

Defining the retention period

15.10 The “retention date” for a specific study is the date following which any remaining documents related to a study will normally be destroyed. The retention date is defined as in the table below.

Scenario	**Retention date**
Invalid application	12 months from the date of sending the letter to confirm application considered invalid
Application withdrawn by Chief Investigator or sponsor prior to final opinion	3 years from the date of acknowledging notification of withdrawal
Application deemed withdrawn by REC due to failure to respond to provisional opinion	3 years from the date of sending letter to confirm application deemed withdrawn
Study abandoned prior to commencement	3 years from the date on which the REC is notified (see paragraph 10.7)
Study terminated early by sponsor	3 years from the date of early termination as notified by the sponsor
Study halted following termination of favourable opinion by REC (non- CTIMPs only)	3 years from the date of sending letter to confirm termination of opinion
Study halted following termination of regulatory approval by MHRA or other relevant body	3 years from the date of the termination of regulatory approval
Study completed	5 years from the date of the conclusion of the study (as notified by the sponsor in the end of study declaration)

Study documentation to be retained by the REC

15.11 The following documents should be retained by the REC at least until the retention date:

- REC application form and all accompanying documentation (including any revised versions provided during initial review).
- Notices of substantial modification and all accompanying documentation (including any revised versions provided during ethics review).
- Reports of UK SUSARs submitted since the most recent annual safety report and line listing (CTIMPs).
- All reports of Serious Adverse Events (non-CTIMPs).
- The latest version of the Investigator's Brochure where applicable (CTIMPs only).
- Annual safety reports (CTIMPs only).
- Annual progress reports (If relevant).
- Reports of actual or alleged serious breaches, and any related documentation or correspondence.
- Other reports submitted by the sponsor, e.g. reports from Data Monitoring Committees.
- Declaration of the conclusion or early termination of the study.
- All correspondence with the sponsor, Chief Investigator on the initial application, appeals, substantial modifications, safety reports or other matters relating to the conduct or management of the study.
- Any correspondence about the study with study participants or individuals or groups representing participants, patients or service users.

- Any correspondence with other regulatory or governance bodies about the study.
- Any correspondence with referees including all reports and comments provided by referees.

Back to Contents

ANNEX A: Definition of a Clinical Trial of an Investigational Medicinal Product (CTIMP)

The Regulations only apply to clinical trials of investigational medicinal products (CTIMPs).

“Medicinal products” are substances or combinations of substances which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis or to restore, correct or modify physiological functions in humans.

A “clinical trial” is an investigation in human participants which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.

Clinical studies involving only food supplements or other non-medicinal therapies (such as surgical interventions) are not covered by the Clinical Trials Regulations.

Clinical investigations of medical devices are not generally covered by the Clinical Trials Regulations but may require a separate form of authorisation under the Medical Devices Regulations 2002 (see paragraph 14.39). It should be noted, however, that some medical devices may also be medicinal products and, if so, both sets of Regulations may apply.

Further guidance on this may be sought from the Clinical Trials Unit at the MHRA.

The Regulations do not apply to “non-interventional trials”. A non-interventional trial is one in which all of the following conditions are met:

(a) the products are prescribed in the usual manner in accordance with the terms of that authorisation;

(b) the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a clinical trial protocol.

(c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study;

(d) no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of the particular therapeutic strategy in question;

(e) epidemiological methods are to be used for the analysis of the data arising from the study.

Back to Contents

ANNEX B: Notification of substantial modifications to CTIMPs

The sponsor of a clinical trial of an investigational medicinal product (CTIMP) is required to notify substantial modifications to the MHRA and/or the REC.

The sponsor must indicate on the modification whether the request is for:

- Authorisation by the competent authority, or
- Favourable opinion from the ethics committee, or
- Both authorisation and a favourable ethics opinion.

Where a substantial modification is for review of one body only, there is no requirement to notify the other body for information.

It is the responsibility of the sponsor to decide whether a modification meets the criteria for a substantial modification, and if so whether it requires authorisation and/or an ethics opinion. However, sponsors may wish to take account of the following general guidance, which has been agreed between RES and the MHRA.

Modifications normally requiring authorisation only

- New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator.
- Changes to the reference safety information for the annual safety report.
- Changes to the Investigational Medicinal Product Dossier (further guidance is in Chapter 8 of the CHMP Guideline on the requirements for chemical and pharmaceutical quality documentation concerning IMPs in clinical trials.
- Reduction in the sponsor's planned level of monitoring for the trial.

Modifications normally requiring a favourable ethics opinion only

- Significant[6] changes to participant information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, etc. (whether generic to the whole study or specific to a particular trial location).

[6] "Significant" in this context means likely to affect to a significant degree the safety or physical or mental integrity of trial participants or the scientific value of the trial, or otherwise significant.

- Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial.
- Significant increase or decrease to the radiation exposures to participants from the protocol.
- Change of insurance or indemnity arrangements for the trial.
- Change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.
- Change of the Chief Investigator.
- Change to the definition of a trial location.
- Any other significant change to the conduct or management of the trial at particular trial locations.
- Any other significant change to the terms of the original REC application.

Modifications normally requiring both authorisation and a favourable ethics opinion

- Change of the main objective of the trial.
- Change of primary or secondary endpoints likely to have a significant impact on the safety or scientific value of the trial.
- Use of a new measurement for the primary endpoint.
- Protocol modifications due to new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment.
- Addition of a trial arm or placebo group.
- Significant change of inclusion or exclusion criteria (e.g. age range) likely to have a significant impact on the safety or scientific value of the trial.
- Change of a diagnostic or medical monitoring procedure likely to have a significant impact on the safety or scientific value of the trial.
- Withdrawal of an independent data monitoring committee.
- Change of IMPs.
- Change of dosing of IMPs.

- Change of mode of administration of IMPs.
- Any other change of study design likely to have a significant impact on primary or major secondary statistical analysis or on the risk/benefit assessment.
- Temporary halt of the trial or temporary halt at a trial location, and re-start of the trial following a temporary halt.
- Change of the definition of the end of the trial.

Modifications of an important detail

- Changes to the identification of the trial (e.g. change of title).
- Increase in duration of the trial, provided that the exposure to treatment is not extended, the definition of the end of trial is unchanged and there is no change to monitoring arrangements.
- Changes of Investigator (other than the Chief Investigator) at a trial location in a multi-centre trial (The expectation is that sponsors will have arrangements in place to ensure selection of suitable locations and investigators.
- Changes to contact details for named contacts for the trial, for example the sponsor, sponsor representative or chief investigator.
- Addition of new trial locations not listed with the original request for authorisation and REC application where there are no additional documents for submission.
- Changes to a protocol approved under the 2004 Clinical Trial Regulations that are only to provide alignment with the 2025 Clinical Trial Regulation requirements, including technical or organisational measures
- Change of the sponsor's legal representative
- Change of the sponsor. It is not a legal requirement for the REC to consider the suitability of the sponsor. However, if the change in sponsor would require changes to insurance arrangements and/or study documents (beyond only changing the name of the sponsor within study documents) then this would be a substantial modification
- Inclusion or withdrawal of another country in the UK.

Minor Modifications

- Changes in the number of participants per trial location, if any change is insignificant in view of the absolute number of participants (determining whether a change is significant or insignificant is the responsibility of the sponsor).

- Changes in the processes associated with recording keeping used by the research team for recording trial data
- Internal changes to the sponsor's organisation
- Changes to the logistical arrangements for transporting or storing samples.
- Changes to technical equipment.
  Minor changes to the protocol or other study documentation, for example correcting errors, updating contact points, minor clarifications.

The issue of an updated Investigator's Brochure or Summary of Medicinal Product Characteristics for the IMP is not itself regarded as a substantial modification unless it includes changes that would meet the criteria for a substantial modification. There is no requirement to provide the MHRA or REC with updated versions of the Investigator's Brochure or SMPC routinely or to seek authorisation or an ethics opinion.

Back to Contents

ANNEX C: Corrective procedures following a legally invalid ethics opinion on a CTIMP

1. This Annex sets out the corrective action to be taken where evidence emerges that a CTIMP is not compliant with the Clinical Trials Regulations because the opinion given by the ethics committee is not legally valid. This could be for a number of reasons, including:

    - The trial was reviewed by a committee not recognised by UKECA ("authorised committee");
    - The trial was submitted as a non-CTIMP and the opinion was based on an invalid application;
    - The trial was reviewed by a recognised committee but without the appropriate recognition for the type of trial;
    - The ethics review process breached the quorum requirements as set out in the Clinical Trial Regulations.

2. Such non-compliances are referred to in this annex as "invalid ethics opinions". They will normally come to light as a result of an audit of the ethics committee undertaken by RES or another body. Exceptionally, they may be reported by the sponsor following its own audit or identified by the MHRA's GCP Inspectorate.

3. Any information relating to a possible invalid ethics opinion should initially be sent to the Operational Manager for further investigation. If it is confirmed that there has been non-compliance, the Operational Manager will take the following action as soon as possible:

    (i) Initiate corrective action to ensure the trial has a valid ethics opinion, following further review of the trial where appropriate;

    (ii) Notify the Clinical Trials Unit and the GCP Inspectorate of the non-compliance within 7 calendar days of the matter coming to their attention and the corrective action being taken by the Research Ethics Service as a follow up report; and

    (iii) Notify the sponsor and give advice about the action it should take.

4. The corrective action to be taken by the ethics committee system and the sponsor will depend on the type of non-compliance and the level of risk, if any, posed to the safety and well-being of trial participants. As a general rule, the following steps will be

appropriate. Where doubt arises, the Operational Manager should seek advice from the Head of the CTU.

Trial submitted as a CTIMP and favourable opinion given by a REC without the appropriate type of recognition

5.1 If a Trial is submitted as a CTIMP and a favourable opinion is given by non-recognised committee or a committee without the appropriate type of recognition:

(i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants

(ii) The Operational Manager should identify an appropriate committee, secure an early agenda slot, transfer the application to the second committee and notify the sponsor of the submission arrangements.

(iii) The Operational Manager should notify the MHRA within 7 calendar days of the matter coming to the attention of the REC and confirm the corrective action taken in a follow up report.

(iv) The sponsor should submit a substantial modification to the MHRA as a serious breach, notifying voluntary suspension of the trial and the corrective action being taken.

(v) When a new favourable opinion is obtained, the sponsor should submit a further substantial modification to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from participants.

(vi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.

Trial submitted and reviewed as a non-CTIMP, and it is later confirmed by MHRA it is a CTIMP

5.2 If a Trial is submitted and reviewed as a non-CTIMP, and it is later confirmed by the MHRA that it is a CTIMP:

(j) The Approvals staff/REC Manager should liaise with the MHRA to establish whether the trial has clinical trial authorisation (CTA);

(ii) If the trial does not have CTA, the sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health

of participants, and prepare an application to the MHRA;

(iii) In all cases, action should be taken as below to confirm a valid ethics opinion.

Where the trial was submitted as a non-CTIMP and reviewed by a REC with appropriate recognition for the type of CTIMP

(iv) If CTA is in place, the trial may continue pending confirmation of a valid ethics opinion;

(v) The sponsor should submit a substantial modification to the REC, enclosing an updated REC application form correctly identifying the study as a CTIMP.

(vi) A copy of the CTA letter should be enclosed with the substantial modification or forwarded as soon as available;

(vii) The substantial modification and accompanying documentation should be reviewed by a sub-committee including at least the Chair and a pharmacist member as a minimum;

(viii) Any additional information or clarification may be requested from the sponsor in writing within the 35-day review period;

(ix) A new final opinion letter should be issued, and the status of the study changed to a CTIMP in HARP;

(x) Exceptionally, if there is ethical objection the matter should be discussed at a meeting of the full committee, and further procedural guidance should be sought from the Operational Manager in consultation with senior staff at the MHRA;

Where a trial was submitted as a non-CTIMP and reviewed by a REC, without the appropriate type of recognition, and is later confirmed by MHRA it is a CTIMP

(xi) A CTA application should be submitted the MHRA as soon as possible.

(xii) The Operational Manager should identify an appropriate committee, secure an early agenda slot, transfer the application to the second committee and notify the sponsor of the submission arrangements.

(xiii) The Operational Manager should notify the MHRA within 7 calendar days

of the matter coming to the attention of the REC and confirm the corrective action taken in a follow up report.

(xiv) The sponsor should submit a substantial modification to the MHRA as a serious breach, notifying voluntary suspension of the trial and the corrective action being taken.

(xv) When a new favourable opinion is obtained, the sponsor should submit a further substantial modification to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from participants.

(xvi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.

Non-compliance with requirements of Regulation 9 (regarding REC constitution)

5.3 If the ethics review process breached the quorum and constitution requirements as set out in Regulation 9 of the Clinical Trial Regulations:

(i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants

(ii) The Operational Manager should identify an appropriate REC, secure an early agenda slot, transfer the application to the second committee and notify the sponsor of the submission arrangements.

(iii) The Operational Manager should notify the MHRA of the non-compliance within 7 calendar days of the matter coming to the attention of the REC. They should also inform the MHRA of the corrective action taken in a follow up report.

(iv) The sponsor should submit a substantial modification to the MHRA as a serious breach, notifying voluntary suspension of the trial and the corrective action being taken.

(v) When a new favourable opinion is obtained, the sponsor should submit a further substantial modification to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from participants.

(vi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.

Back to Contents

ANNEX D: Insurance, indemnity and compensation

Legal requirements

1. The REC is required by the Clinical Trials Regulations to consider provision for indemnity or compensation in the event of injury or death attributable to a CTIMP, and any insurance or indemnity to cover the liability of the investigator and sponsor(s). Schedule 3 to the Regulations puts the onus on the applicant to provide information about the financial arrangements for the trial, including any provision for compensation, details of any insurance or indemnity, and summary details of any financial arrangements between the sponsor (or funder) and the investigator and the trial location.

2. In the case of any research study it reviews, the REC should be reassured about the insurance and indemnity arrangements and consider provision in proportion to the risk for compensation or treatment in the event of injury, disability or death attributable to participation in the research. Before confirming a favourable opinion on any research (including both CTIMPs and non-CTIMPs), the REC should assure itself that the sponsor and investigators will have appropriate insurance or indemnity cover for the potential legal liability arising from the research. For studies taking place within the NHS/HSC, RECs can take assurance that the insurance and indemnity arrangements will have been checked as part of the study wide review. For specific guidance on Phase 1 trials, see paragraphs 18 below.

3. Applicants must provide information to show that there are adequate insurance or indemnity arrangements to cover potential legal liability arising from the management, design and conduct of the research. Applicants must show that:

    - the arrangements cover the research study concerned;
    - the sponsor and, except for Phase 1 trials, all protocol authors, investigators/collaborators and, where applicable, Location Management Organisations will all be protected by insurance or indemnity arrangements;
    - the arrangements will provide adequate cover to meet the potential liability assessed by the sponsor.

4. The sponsor should sign the declaration in the application form to confirm that any necessary insurance or indemnity arrangements will be in place before the research starts.

5. RECs are not expected to undertake detailed expert scrutiny of insurance policies. The responsibility for ensuring that cover is adequate lies with sponsors themselves. Committees should expect the application to include coherent written assurances about the financial arrangements that the committee can reasonably rely on. Where there is any reason to be concerned about the information provided, it is encouraged to seek a further explanatory statement from the sponsor clarifying what exactly any insurance policies or indemnities provide when taken together, the basis on which the quantum of cover has been determined, and the relevant arrangements between the parties.

6. For CTIMPs, it is not acceptable for a commercial sponsor to provide an undertaking to "self-insure" against the potential liability from its own funds. The insurance or indemnity must be provided by another legal entity. It is acceptable for the insurer to be another company within the same corporate group provided it is a separate legal entity.

7. NHS organisations acting as sponsors or co-sponsors of research, and Chief Investigators, Principal Investigators and other staff involved in designing or conducting research within the terms of substantive NHS employment contracts, will normally have access to the NHS indemnity schemes. Provision of indemnity through NHS schemes will be ensured when final management permission is given for the research by the care organisation. NHS research governance processes can be relied on for this purpose and it is not necessary for the applicant to provide documentary evidence of NHS indemnity with the application. However, the application should make clear the extent to which NHS indemnity will apply to the research. For example, in a commercially sponsored study at a mix of NHS and non-NHS locations, investigators employed by the NHS would be covered by NHS indemnity, but separate insurance or indemnity cover would be required for the sponsor and any investigator who is conducting the research at a non-NHS location, including independent practitioners recruiting private patients. (For guidance on independent practitioners recruiting NHS patients, see paragraph 12 below.)

Compensation for harm where liability does not arise

8. In the case of commercially sponsored CTIMPs or medical device studies, compensation to participants where liability does not arise ("no fault compensation") will normally be available under the Association of British Pharmaceutical Industry (ABPI) or Association of British Healthcare Industry (ABHI) schemes. Where this applies, the applicant should provide the REC with a clear statement of the policy for

the trial on the application form, confirming that the relevant ABPI/ABHI guidelines will be followed, and a copy of the model form of indemnity to be used.

9. It is not necessary for the REC to be provided with a copy of each signed form of indemnity produced under the ABPI or ABHI schemes as part of the Clinical Trial Agreement between the sponsor(s) and the relevant care organisation. This process will generally be finalised shortly before final management permission for the research is given by the care organisation.

10. For research other than CTIMPs and clinical investigations of medical devices, there are no guidelines on whether provision for no-fault compensation should be in place. It is an ethical issue for the sponsor and the REC to consider on a case by case basis, considering the potential risk to participants and whether or not the sponsor is in a position, legally and financially, to make such an undertaking. RECs should bear in mind that it is 'ultra vires' for NHS organisations to offer advance compensation to participants for harm where no liability arises. The possibility of no-fault compensation should not be mentioned in information sheets unless the sponsor has a formal scheme in place backed by adequate insurance or indemnity arrangements.

The position of independent practitioners

11. In England and Wales, GPs and practice staff (for example, practice nurses) are covered under the scope of the Clinical Negligence Scheme for General Practice (England) or the Clinical Negligence Scheme for Providers of Primary Medical Service (Wales).

12. In Scotland and Northern Ireland, GPs are usually independent practitioners who provide services under contract with the Clinical Commissioning Group (i.e. they are not salaried employees). As such, they are not covered by NHS indemnity and must have their own personal indemnity arrangements. Other independent practitioners (across the whole of the UK) to whom this applies include dentists, optometrists and community pharmacists. Independent practitioners will normally arrange indemnity cover for their clinical practice through their professional bodies or mutual defence organisations such as the Medical Defence Union. Cover will normally extend to private practice as well as NHS practice. NHS staff employed by these independent practitioners (for example, practice nurses) are not covered by NHS indemnity but will normally be covered by the practitioner's professional indemnity arrangements.

13. Some GPs are salaried employees of NHS care organisations. They will be covered by NHS indemnity when the care organisation gives management permission for the

research.

14. Where independent practitioners conduct research involving NHS/HSC patients, the NHS/HSC care organisation will ensure that appropriate indemnity arrangements are in place for independent practitioners before giving management permission. The REC system may rely on the research governance process for this purpose. RECs undertaking main ethics reviews are not therefore required to seek separate evidence of insurance or indemnity cover for independent practitioners who are participating in research involving NHS patients.

15. Where the research involves private patients (and is therefore not subject to NHS research governance), the REC is responsible for ensuring that appropriate indemnity arrangements are in place. RECs undertaking the main ethics review should seek the following:

    - A copy of the indemnity policy for the Chief/Principal Investigator (as applicable), and
    - A written assurance from the practitioner that the policy provides cover for the research or, if not, written confirmation from the indemnity provider that the cover will be extended.

16. Professional indemnity will normally provide adequate cover for research procedures which are equivalent to services normally offered by the practitioner to their NHS patients, for example:

    - assessing patients against defined inclusion/exclusion criteria;
    - referring or recruiting patients to research;
    - screening patients and taking informed consent;
    - initiating or undertaking specified tests or investigations that form part of routine clinical practice;
    - delivering clinical interventions within a research study, where those interventions are accepted examples of normal care within their clinical practice (e.g. licensed medicines or UKCA/CE UKNI/CE-marked medical devices being used within their normal intended purpose).

17. However, professional indemnity would not normally cover the following research activities:

(i) Chief Investigator

Chief Investigators have a range of responsibilities that go beyond normal clinical care, for example protocol design, applying for ethics review, management of the research, data analysis and writing up the results.

Independent practitioners will not be covered by personal professional indemnity for their role as Chief Investigator in any study.

(ii) Research procedures outside normal care

This would include any clinical interventions, tests or investigations that are not accepted examples of normal care within the practitioner's clinical practice. Examples include unlicensed medicines, non-UKCA/CE UKNI/CE-marked medical devices, or licensed medicines or UKCA/CE UKNI/CE-marked devices administered outside the normal conditions of use.

18. In the above circumstances, the practitioner may need to take out additional cover with their insurer.

Insurance and compensation for commercially sponsored Phase 1 clinical trials

19. Guidance on 'Insurance and compensation in the event of injury in Phase 1 clinical trials' ('industry guidance') has been developed by industry bodies in consultation with DH and RES and is published on the Association of the British Pharmaceutical Insurance and compensation in the event of injury in Phase I clinical trials 19. The industry guidance applies specifically to commercially sponsored Phase 1 trials. It applies principally to trials in 'healthy participants' but also extends to 'patient participants' without the target disease).

19. The industry guidance is intended for reference by sponsors, clinical research organisations (CROs) and Research Ethics Committees (RECs). Its purpose is to provide authoritative recommendations on the level of insurance cover and other aspects of insurance, based on industry best practice and review of the history of claims in this field, and to enable sponsors to provide assurance to RECs that adequate insurance is in place to back its undertaking to compensate volunteers on a "no fault" basis.

20. When reviewing such trials, RECs should be assured that the insurance and compensation arrangements made by the sponsor comply with the guidance.

Summary of industry guidance

21. Key points of the industry guidance are as follows:

(i) Under the ABPI Phase 1 guidelines, commercial sponsors of Phase 1 trials in the UK should accept an undertaking to compensate participants in the event of any injury resulting from participation in the trial, irrespective of the volunteer's ability to prove fault on the part of the sponsor or anyone else connected with the study.

(ii) This undertaking should be made clear to participants in the information sheet for the trial, which should also give details about how to make a claim and where to seek further information or assistance if required (including contact details for the relevant trade association).

(iii) The intention of the undertaking is to create a contractually binding commitment on the part of the sponsor.

(iv) The undertaking still applies where the injury may have resulted from the negligence of other parties such as a CRO or an individual investigator or member of their team. Where this applies, the sponsor will fulfil the obligation to compensate the participant upfront and seek to recoup its costs from the other party.

(v) Under the Clinical Trials Regulations, sponsors and investigators are legally required to have insurance or indemnity to meet their potential liability arising from the trial.

(vi) Sponsors must have commercial insurance cover to meet their potential liabilities and to pay upfront any claims arising from the negligence of other parties. 'Self-insurance' based on the sponsor's own financial resources is not considered legally acceptable by DH. The insurance must be provided by another legal entity. It is acceptable for the insurer to be another company within the same corporate group provided it is a separate legal entity.

(vii) It is recommended that sponsors purchase insurance that provides a minimum of £5m indemnity cover for any first-in-human Phase 1 trial, or £2.5m for other Phase 1 trials. These recommendations are based on the history of claims in this field, the level of compensation commonly awarded (under English law or in other parts of the EU) for the types of injury that might be suffered in a Phase 1 trial, and the practices and

capacity of the insurance market.

(viii) The cover should include compensation for ancillary expenses incurred by volunteers such as legal costs but should exclude any expenses incurred by the sponsor.

(ix) Within the aggregate level of cover, there should not be any limit to the indemnity available to an individual volunteer.

(x) Cover may be arranged either through trial-specific policies or 'block' policies. The sponsor must assure the REC that the required level of cover will be in place for the trial concerned. (If a claim was made against a 'block' policy, the sponsor would need to consider whether to purchase additional cover to ensure the required level of cover remained available for other trials.)

(xi) The insurance must allow a **'discovery period'** of at least 3 years, i.e. a claim may be made up to 3 years after the last dose of the IMP received by the volunteer.

(xii) Except for specified standard conditions, which would normally be included in any insurance policy of this type (see paragraph 7 below), sponsors should not insert conditions or exclusions potentially affecting the availability of cover. Where additional conditions are proposed, this should be declared to the REC and justified on the facts of the study.

(xiii) The insurer should be in receipt of appropriate authorisations and registrations governing the conduct of its business and its ability to respond to claims in the UK but does not need to be a UK insurer (i.e. authorised with the Financial Services Authority).

(xiv) Other parties are recommended to take out equivalent insurance cover to meet their own potential liabilities in the event of a claim against them by the sponsor.

Scope of the industry guidance

22. As well as trials in healthy volunteers, the scope of the industry guidance extends to Phase 1 trials including 'patient volunteers', i.e. patients with a chronic but stable condition such as asthma, hypertension or renal impairment, who are recruited to provide additional pharmacokinetic data about the IMP but do not have the disease or condition the IMP is intended to treat.

23. The guidance does not apply to first-in-human trials which, due to the inherent toxicity of the medicine, are undertaken in patients with the disease or condition the IMP is intended to treat (e.g. oncology trials). Such trials are considered by the MHRA to be Phase 2 trials as there is some potential for benefit to the participants. Patients in such trials are covered by the separate ABPI guidelines 'Clinical Trials – compensation for medicine-induced injury' (1991), which apply to the generality of Phase II and Phase III trials.

Standard conditions and exclusions

24. It is normal practice for insurers to include the following standard conditions for liability in clinical trials policies:

    a. Absence of intentional misconduct on the part of the insured;

    b. Meeting the regulatory requirement that the study has been authorised by the competent authorities;

    c. Making proper disclosure of background facts of the proposed study that would be material to the insurer's willingness to accept the risk or his setting of the premium;

    d. Making timely notification of a claim to the insurer and not compromising it without the agreement of the insurer.

Statement of Insurance Cover

25. The industry guidance includes a template for a 'Statement of Insurance Cover' to be submitted to the REC as part of any commercially sponsored Phase 1 trial application. The statement is designed to provide the REC with clear assurances that adequate cover will be in place in line with the industry guidelines.

26. The statement has been incorporated into IRAS and forms a section in Q76 for applications identified in the IRAS Project Filter as commercially sponsored Phase 1 trials.

27. Applicants are required to complete all sections of the statement to satisfy the REC and MHRA that participants who take part in a Phase I trial are adequately protected against injury.

28. Where the application names more than one sponsor, each co-sponsor is expected to make equivalent arrangements and should provide a separate version of the statement.

Guidance on ethics review

29. Staff should ensure that RECs are aware of the following guidance when undertaking reviews of Phase 1 trials and should undertake an initial check of the relevant points to assist the REC.

Compensation policy

30. The answer to Question A77 in IRAS should confirm the sponsor's undertaking to compensate participants on a "no fault" basis in the event of any injury resulting from participation in the trial, in accordance with the ABPI Phase 1 guidelines.

Assurance of insurance cover

31. Staff should check from the Statement of Insurance Cover that:

    a. Indemnity cover is available for the trial as part of a commercial insurance policy with a named insurer;

    b. The aggregate limit of indemnity for the trial is not less than £5m

    c. A discovery period of at least 3 years is allowed;

    d. No additional conditions or exclusions in the policy have been declared beyond the normal conditions mentioned in the industry guidance.

32. Where these normal requirements are met, the REC should be advised – either at the meeting or in a preparatory written brief, in accordance with local practice – that the insurance cover proposed for the trial complies with industry guidance.

33. Where the statement indicates that the insurance cover departs from the industry guidance (e.g. the quantum is lower, the discovery period is shorter, or there are additional conditions or exclusions), the Approvals Specialist/REC Manager should draw this to the attention of the REC. The REC should expect additional justification to be provided in the statement and should consider whether the proposed arrangements are reasonable in the circumstances of the trial.

34. Applicants are not normally required to provide a copy of the insurance policy itself. RECs are not constituted to have expertise in the scrutiny of insurance documents and may rely on clear assurances given by the sponsor in the Statement of Insurance Cover. (It would be an offence under the Clinical Trials Regulations to provide false information to the REC in this statement or any other aspect of the application.) However, a REC may exceptionally request a copy of the policy where it has particular reason to do so, for example, to check the wording of any additional conditions declared by the sponsor.

Volunteer information sheet

35. As part of its review of the consent process, the REC should also check that the volunteer information sheet includes the following:

    a. A clear statement of the sponsor's compensation policy, including the undertaking to compensate the volunteer for any injury resulting from participation in the trial, without the need to prove fault on the part of the sponsor or anyone else connected with the trial;

    b. Information about how to make a claim and where to seek further information or assistance in progressing a claim, including at least a contact point in one of the industry associations (ABPI, BIA, CCRA);

    c. A simple explanation of the process for considering claims, including how compensation would be determined and arrangements for arbitration in case of dispute between the sponsor and the volunteer;

    d. A copy of the ABPI compensation guidelines (in the form of an extract from the Phase 1 guidelines) should be provided to the volunteer with the information sheet;

    e. Volunteers should be invited to seek clarification of any aspect of the guidelines, the sponsor's undertaking to compensate or the claims procedure that is not clear to them.

36. Staff should carry out an initial check of the information sheet and draw the attention of the REC to any changes that might be required. If the REC would otherwise be able to give a favourable opinion of the application, any changes to the information sheet can normally be required through attaching conditions to the opinion.

ANNEX E: Statutory requirements relating to research involving human tissue

The Human Tissue Act 2004

1. The Human Tissue Act 2004 ("the HT Act") is a framework for regulating the storage and use of human tissue from the living, and the removal, storage and use of tissue and organs from the deceased, for specified health-related purposes and public display.

2. The HT Act makes consent the fundamental principle underpinning the lawful retention and use of body parts, tissue and organs from the living or the deceased for specified purposes (known in the Act as "scheduled purposes"). Consent is also required for the removal of such material from the deceased. It does not cover removal of such material from the living – consent for this continues to be required under common law.

3. One of the scheduled purposes under the HT Act is "research in connection with disorders or the functioning of the human body". References to "research" in this Annex and in section 12 of the SOPs mean research included within this definition.

4. The HT Act establishes the Human Tissue Authority (HTA) to advise on and oversee compliance with the HT Act. The Authority issues good practice guidance in the form of Codes of Practice, which are laid before Parliament and are published at http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice.cfm The most important of these for the purpose of ethics review is the Code of Practice on Consent. The HTA will also license and inspect a range of activities including the storage of human tissue for research.

5. Most parts of the HT Act were brought into force on 1 September 2006 by Regulations made under the Act. Except for the provisions on genetic/DNA analysis (see paragraphs 16-18) and storage of relevant material for transplantation, the Act extends to England, Wales and Northern Ireland only.

Definition of relevant material

6. Human tissue and cells are referred to in the HT Act as "relevant material". This is generally defined in the Act as any material that has come from a human body and consists of, or includes, human cells. The HTA defines cells as "individual human cells or a collection of human cells when not bound by any form of connective tissue".

This definition excludes cell lines. Other exceptions to the definition in the Act (except in relation to DNA analysis) are hair and nail of living people, embryos outside the body and gametes. Embryos created outside the body, and gametes, are covered by separate legislation.

7. More detailed guidance on what is, or is not, relevant material is available in a policy statement on the HTA website and in an e-learning module on research and human tissue legislation developed by the Medical Research Council (see http://www.byglearning.co.uk/mrcrsc-lms/course/category.php?id=1).

8. The statutory definition of relevant material should be applied in the same way to the definition of the tissue of NHS patients for the purpose of determining whether ethics review is required under NHS research governance systems and the REC Policy Document.

Consent to use of tissue in research

Legal requirements

9. Under the HT Act there is a general requirement to obtain "appropriate consent" (see paragraph below – 13) in order to store or use human tissue for scheduled purposes. The HT Act provides a number of exceptions to this rule. In relation to research, the most important exceptions are:

(i) Existing holdings

Under section 9 of the HT Act it is lawful to retain and use, without consent, human tissue already held in storage for research purposes on the day before the Act came into effect ("existing holdings"). This applies to tissue from the living or the deceased. It does not however imply that such tissue can be freely used without regard to ethical consideration (see paragraph 12.10 of the SOPs).

(ii) Tissue from the living

Under section 1(9) of the HT Act it is lawful to store and use for research, without specific consent for this purpose, tissue which has been lawfully removed from the living for other purposes, e.g. any surplus (or "residual") tissue taken with consent for diagnostic or therapeutic purposes in the course of normal clinical care and which is left over from these procedures. The conditions are that the research must be ethically approved by a REC or other research ethics authority and the researcher must not be in possession, and not likely to come into possession, of information which would identify the person from whom the tissue came. The exception may also

apply to research undertaken by clinicians using tissue from their own patients, provided that it will be conducted in an anonymised fashion.

(iii) Imported material

It is lawful to store and use for research, without consent, human tissue which has been imported but the importer should comply with the best practice set out in the HTA Code of Practice on the Import and Export of Human Bodies, Body Parts and Tissue.

(iv) 100-year rule

It is lawful to store and use for research, without consent, human tissue from the body of a person who died before 1 September 2006 and at least 100 years have elapsed since their death.

10. Consent continues to be required under the common law to remove any bodily material from living persons. In some cases, consent may explicitly be sought to remove the tissue for research purposes. Alternatively, consent may be sought to remove the tissue for diagnostic or therapeutic purposes; the surplus tissue may then be used lawfully in research without specific consent subject to the conditions in section 1(9) of the HT Act (see 9(ii) above).

11. Table 1 summarises legal requirements under the HT Act and the common law for consent to remove, store or use tissue, or analyse DNA in bodily material, for research purposes. (In relation to DNA analysis, bodily material includes the hair and nail of living persons and gametes.) It should be noted that, even where there is no legal requirement for consent, there still is a requirement to hold a licence from the HTA to store the tissue for use in research or to seek/obtain ethics approval to qualify for exemption from licensing (see paragraphs 27-29).

Table 1: Summary of legal requirements for consent to remove, store or use tissue or analyse DNA in bodily material for research purposes

Scenario	Consent legally required?
Storage or use of existing holdings	No
Analysis of DNA in existing holdings	No
Storage or use of imported tissue	No (but good practice for importer to seek evidence of consent – see HTA Code of Practice)
Storage or use of tissue from a deceased person who died more than 100 years ago	No
Storage or use of tissue from the living (not identifiable to the researcher)	No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)
Analysis of DNA in tissue from the living (not identifiable to the researcher)	No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)
Storage or use of tissue obtained from a deceased person who died less than 100 years ago	Yes
Storage or use of tissue from the living (identifiable to the researcher)	Yes
Removal of tissue from the living	Yes (under common law)
Removal of tissue from the deceased	Yes
Analysis of DNA in tissue from the living (identifiable to the researcher)	Yes

Analysis of DNA in tissue obtained after 1 September 2006 from a deceased person who died less than 100 years ago	Yes

12. On consent practice, the HTA encourages gifting of tissue in research to be sought at the outset from donors as the default position. This allows tissue to be used for different research projects over an unspecified period of time and mitigates the need to obtain repeat consent for each and every research project. Further guidance is available in the HTA Code of Practice on Consent.

Appropriate consent

13. The HT Act identifies the person who can give "appropriate consent" where this is required for lawful storage or use of tissue for research. Table 2 summarises who can give appropriate consent under the Act.

Table 2: Appropriate consent

The person	Who gives consent?
Living adult, or living child[11] with capacity and willing to make a decision	His/her own consent
Living child[11] who lacks capacity to give consent or who has capacity but is unwilling to make a decision	A person with parental responsibility
Deceased adult	• His/her own consent before death. • If no prior consent by the deceased adult, the consent of a nominated representative. • If no representative was appointed by the deceased person, a person in a qualifying relationship.

Deceased child[7]	• A person who had parental responsibility immediately before the child's death. • If no person had parental responsibility, another person in a qualifying relationship.
Living adult who lacks capacity to give consent	See paragraph 15 below.

[7] The HT Act defines a child as a person under the age of 18.

14. Persons in a qualifying relationship are ranked in the following order where consent is sought to store or use human tissue from the deceased:

    (a) Spouse or partner (including civil partners).

    (b) Parent or child.

    (c) Brother or sister.

    (d) Grandparent or grandchild.

    (e) Child of a brother or sister.

    (f) Stepfather or stepmother.

    (g) Half brother or half sister.

    (h) Friend of long standing.

15. Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.

Consent to analysis of DNA (applies also in Scotland)

16. The HT Act makes it an offence to have human tissue (which in this particular context includes the hair and nail of living persons and gametes) with the intention of analysing its DNA or using the results of the analysis without consent unless for an excepted purpose. This provision applies UK-wide. However, the effect of the exceptions is that it is not an offence to analyse DNA without consent in research if any of the following apply:

    - The tissue is an existing holding (i.e. held before 1 September 2006) and the results of the analysis are to be used for the purposes of research.
    - The tissue is obtained on or after 1 September 2006 from the body of a living person and the researcher is not likely to come into possession of the identity of the donor and the research is ethically approved.
    - The tissue is an embryo outside the human body.
    - The tissue is from the body of a person who died before 1 September 2006 and at least 100 years have elapsed since their death.

17. Therefore, consent **is** required to analyse DNA or use the results of the analysis for research purposes in each of the following cases:

- The tissue is obtained on or after 1 September 2006 from a living person in the UK and the researcher knows, or is likely to know, the identity of the donor.
- The tissue is obtained on or after 1 September 2006 from a living person in the UK and the research is not ethically approved.
- The tissue is obtained on or after 1 September 2006 from a deceased person who died before 1 September 2006 and less than 100 years have elapsed since their death.
- The tissue is obtained from a deceased person who died on or after 1 September 2006.

18. Where consent is required, the requirements for "qualifying consent" are similar to those for "appropriate consent" in the case of tissue (see paragraphs 13-14). However, for the purpose of consent to analyse the DNA in the tissue of a deceased person, the consent of any person in a qualifying relationship is enough – the list of relatives is unranked in this case.

19 The HT Act does not cover DNA analysis from 'non-relevant material', such as serum. A joint statement has been produced between the HTA and the HRA which advises that as the same ethics issues arise as with DNA analysis from relevant material, the same review process should apply. Therefore, applications for research which involve analysis of DNA extracted from 'non-relevant material' should be submitted to a REC for ethics review.

Adults lacking capacity

20. Where consent is required to store or use relevant material from the living, or analyse DNA, in research but the person is an adult (aged 16 or over) without the capacity to give consent, The Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants) Regulations 2006 provide that the adult is 'deemed' to have given consent where the activity is undertaken for the purpose of:

- A CTIMP - the trial is authorised and conducted under the Clinical Trials Regulations, considering the conditions and principles applying to participants lacking capacity under Schedule 1 Part 5 of those Regulations, including the requirement for consent by a legal representative.
- Any other 'intrusive research' in England and Wales - the research is

approved by an 'appropriate body' under Sections 30 or 34 of the Mental Capacity Act 2005, as applicable, taking account of the requirement to seek advice from a consultee.

- Any other research in Northern Ireland – the research has ethics approval from a REC taking into account the following conditions:

  (i) the research is in connection with the disorders, or the functioning of, the human body;

  (ii) research of comparable effectiveness could not be carried out if confined to persons with capacity to consent;

  (iii) research of comparable effectiveness could not be carried out using tissue anonymised to the researcher.

- Any other research requiring consent for analysis of DNA in Scotland - the research is approved under the Adults with Incapacity (Scotland) Act 2000, taking account of the requirement for consent from a guardian, welfare attorney or the adult's nearest relative.

21. For further guidance on approval for research involving adults lacking capacity, refer to Section 13 of SOPs.

Further guidance on consent

22. The HTA Code of Practice on Consent gives detailed guidance on issues of consent under the HT Act. It explains the legal requirements in detail but goes further in establishing standards for obtaining consent and promoting good practice. The Codes of Practice are not legally binding, but their advice represents best practice and should be considered carefully by all those concerned, including tissue bank managers, researchers and ethics committees. The HTA may take account of adherence to the Codes of Practice when it makes licensing decisions.

23. A summary of the consent provisions of the Act is also available in the e-learning module developed by the Medical Research Council (see paragraph 7).

Licensing

24. The HTA has powers under the HT Act to license a range of activities involving human tissue in England, Wales and Northern Ireland, and to conduct inspections to ensure compliance with the Act, codes of practice and licensing conditions. The HTA has no licensing role in Scotland.

25. The activities for which a licence is required include:

- Removal of relevant material from the body of a deceased person for research purposes (unless the person died at least 100 years ago).
- Storage of relevant material from the living or the deceased for use for research purposes (except as specified in paragraphs 27-29).

26. Storage of relevant material is exempt from the licensing requirement where it is 'incidental to transportation', for example in relation to movement of samples from one establishment to another. The guidance from the Human Tissue Authority is that this exemption also applies to temporary storage of relevant material pending processing to render it acellular (e.g. to extract plasma, serum or DNA), provided that any residual relevant material is then disposed of and this process is completed within hours or days, or at most a week. For example, where a research project at a university involves taking blood samples from healthy volunteers but these are then processed to extract plasma samples for research and the blood samples are not retained, this activity does not need to be carried out under the authority of a licence (or seek REC approval as an alternative – see paragraph 27).

Exemption for ethically approved research

27. Under the Regulations made under the HT Act, storage of tissue is exempt from the licensing requirements where it is:

- For the purpose of a specific research project which is ethically approved (including where ethics approval was given before the commencement of the HT Act).
- For the purpose of a specific research project for which an ethics approval is pending (i.e. an application for ethics approval has been submitted but a final opinion has not yet been given).

28. An ethics approval for this purpose may be given by any REC within the UK Health Departments' Research Ethics Service, or any other REC recognised under the Clinical Trials Regulations (which therefore also includes MoDREC).

29. The effect of these provisions is that licences must be held for premises where research tissue banks are storing tissue for unspecified research projects, but licences are not required where end user researchers are holding tissue for specific ethically approved projects.

NHS diagnostic archives

30. Purely diagnostic archives do not need to be stored on HTA-licensed premises.

However, where a diagnostic archive invites applications for release of samples and/or in any way advertises the archive as a research resource, it is functioning as a research tissue bank and must be encompassed within the licensing framework.

31. Diagnostic archives may make voluntary applications for ethics review as a research tissue bank under Section 11 of SOPs. More detailed guidance about licensing, ethics review and consent issues relating to release of tissue from diagnostic archives is in a joint position statement from the RES and HTA, available here

Licensing applications

32. The HTA issue licences to store tissues or cells for research purposes following a process of self-assessment by the establishment (in the form of a Compliance Report) and review by the Authority. The authority conferred by a licence is given to the "Designated Individual" (the person under whose supervision the licensed activity is to be undertaken), any other designated person, and any person acting under the direction of the Designated Individual or a designated person. The Designated Individual has a statutory duty to ensure the suitability of the persons and premises covered by the licence and that all conditions are complied with. More information is available in the HTA's guide to licensing for Designated Individuals and Licence Holders.

33. Compliance reports provide information to the HTA on how the establishment meets the requirements of the HT Act and standards of good practice in the following areas:

- Consent
- Governance and quality systems
- Premises, facilities and equipment
- Disposal

34. Further detailed guidance about licensing requirements is available on the HTA website.

Human Tissue (Scotland) Act 2006

35. The Human Tissue (Scotland) Act 2006 (referred to in this section as "the Act") includes certain provisions relating to research using tissue and organs from the deceased. Unlike the Human Tissue Act 2004 it does not deal at all with research using tissue from the living.

36. Detailed guidance on the Act has been issued by the Scottish Executive in HDL

(2006) 46, which is available on the Scottish NHS website.

The following paragraphs provide an overview of the provisions relating to research.

Authorisation to use human tissue for research

37. Under Section 3 of the Act, part of the body of a deceased person may be removed from the body and used for certain purposes (including research) where the removal and use for this purpose is "authorised". Sections 6-10 of the Act make detailed provisions for such authorisation:

- Section 6 provides for authorisation by an adult of the removal and use of part of the adult's own body after death.
- Section 7 provides for authorisation by the nearest relative of a deceased adult.
- Section 8 provides for authorisation by a child aged 12 or over of the removal and use of part of the child's body after death.
- Section 9 provides for authorisation by a person with parental rights and responsibilities in respect of a child who has died aged 12 or over.
- Section 10 provides for authorisation by a person with parental rights and responsibilities in respect of a child who has died under the age of 12.

38. The above provisions do not apply in relation to tissue samples and organs removed during post-mortem examinations. Nor do they apply to the body of a deceased person who died before 1 September 2006 and at least 100 years have elapsed since their death.

39. Under Section 38, a tissue sample removed from the body of a deceased person (or from an organ removed from the body) during a post-mortem examination and no longer required by the Procurator Fiscal becomes part of the medical records of the deceased persons. Section 39 allows such samples to be used for certain purposes (including research) where use for this purpose is authorised. Sections 42-46 contain provisions for authorisation similar to those in Sections 6-10.

40. Under Section 40 of the Act, an organ removed from the body of a deceased person during a post-mortem examination and no longer required by the Procurator Fiscal may be retained and used for certain purposes (including research) provided that:

- The subsequent use of the organ for this purpose is authorised in accordance with Sections 42-46*,* and
- The research is approved in writing by such persons or groups as the Scottish Ministers may specify (see paragraph 43 below).

41. Under Scottish law a child is defined as a person aged under 16.

Ethics approval

42. Under Section 40 of the Act, research must be approved in writing by such persons or groups as the Scottish Ministers may specify where it involves the use of an organ retained from a post-mortem examination carried out on or after 1 September 2006 on the instructions of the Procurator Fiscal. Under the Approval of Research on Organs No Longer Required for Procurator Fiscal Purposes (Specification of Persons) Scotland Order 2006 such approval must be given by a Research Ethics Committee. The Order also requires Research Ethics Committee approval for new research on organs retained from a post-mortem examination that took place before 1 September 2006. A “research ethics committee” is defined in the Order as:

- Any ethics committee established or recognised under the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, or
- Any other committee established to advise on the ethics of research investigations in human beings and recognised for that purpose by or on behalf of the Secretary of State or the Scottish Ministers. This means all NHS RECs in Scotland and England.

43. The Human Tissue (Scotland) Act 2006 does not require REC approval where the research involves tissue blocks and slides retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal, or tissues and organs retained from a hospital post-mortem examination, and there is authorisation for its use in research (see below). However, under guidance issued on the Act in Scotland those responsible for the research project would be expected to obtain REC approval.

44. Section 48 makes transitional provision for research using organs removed from the deceased during a post-mortem examination carried out on the instructions of the Procurator Fiscal before 1 September 2006 and held for research purposes. Provided that the organ is held for research approved by a REC prior to 1 September 2006, this research may lawfully continue without the need to obtain authorisation in the terms of the Act or any further approval. It may also be used for new research approved by a REC after 1 September 2006 (see paragraph 42).

Back to Contents

ANNEX F: The Social Care Research Ethics Committee

1. The Social Care REC reviews adult social care research and some applications for social sciences research. It is part of the Research Ethics Service (RES), and its membership, expertise and procedures have been developed to reflect the social care context. The Appointing Authority is the Health Research Authority (HRA). Committee members, recruited through open advertisement, include researchers, ethicists, providers and users of social care. In addition to the Social Care REC, a number of NHS RECs are also flagged to review social care research.
2. RECs with the social care flag review applications involving the social care sector (e.g. in local authority, private and voluntary care settings) that would not otherwise have access to ethics review, or which cross sector boundaries. RECs with the social care flag generally expects to review the following types of study:
    - 2.1 Social care research funded by the Department of Health and Social Care (England) involving adult social care service users as participants; and social care research funded by Health and Care Research Wales involving adult and children social care service users as participants.
    - 2.2 Social care research that involves adults lacking capacity in England and Wales and requires approval under the Mental Capacity Act 2005. Social Care flagged RECs in England and Walesare recognised by the Secretary of State and the Welsh Ministers as an Appropriate Body for this purpose.
    - 2.3 Social care research involving the social care sector (e.g. in local authority, private and voluntary care settings) where investigators do not have access to other ethics review systems. This could include service user-led research.
    - 2.4 Studies of integrated services (health and social care), if there is no clinical intervention involved. (this exclusion applies to the Social Care REC only. Other RECs flagged to review social care research can review studies which involve clinical interventions).
    - 2.5 Intergenerational studies in social care, where both adults and children, or families, are research participants.

Exceptions

Social care research does not require review by RECs with the social care flag if it is reviewed by another committee operating in accordance with the Economic and Social Research Council's (ESRC's) Framework for Research Ethics, unless the categories

2.1 to 2.5 apply or the research also involves NHS patients or service users as

research participants. A review is required by REC flagged for social care if there is a legal requirement for REC review as per the REC Policy Document. Student research within the field of social care should ordinarily be reviewed by a University REC (UREC).