Standard Operating Procedures
for
Research Ethics Committees

Version 5.1  March 2012
STANDARD OPERATING PROCEDURES

Contents

Note: At the beginning of each section of the SOPs there is a brief summary of its contents and main points. These are intended as introductions for users and do not explain the standard operating procedures of that section in detail. They should not be cited as an authoritative part of the SOPs.

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[Note: paragraphs 1.22-1.23 were deleted by Amendment No. 1 to Version 5.0]

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Introduction to REC SOPs – version 5.0

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.

2. Under the UK Health Departments’ Governance Arrangements for Research Ethics Committees (GAfREC) (issued on 9 May 2011 and coming into effect on 1 September 2011), 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 National Research Ethics Service in England (NRES) within 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 appointing authorities for, all RECs that are established in accordance with GAfREC. These RECs are:
   - All RECs appointed within the National Health Service and the Northern Ireland Health and Social Care Service (“NHS RECs”)
   - The Gene Therapy Advisory Committee (GTAC)


6. The EU Directive is incorporated into UK law by means of The Medicines for Human Use (Clinical Trials) Regulations 2004 (“The Clinical Trials Regulations”), which came into effect on 1 May 2004. NRES 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.

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 National Institute for Social Care and Health Research (NISCHR) (Wales) and the R&D Division, Public Health Agency (Northern Ireland).

2 The EU Directive is incorporated into UK law by means of The Medicines for Human Use (Clinical Trials) Regulations 2004 (“The Clinical Trials Regulations”), which came into effect on 1 May 2004. NRES 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. In a separate Directive (Commission Directive 2005/28/EC), the European Commission has set out principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as requirements for authorisation of the manufacturing and importation of such IMPs.
7. The policy of the UK Health Departments is that the operating procedures required by the EU Directive and the Clinical Trials Regulations should also apply in general to the review by RECs in the UK of all other health and social care research reviewed under GAfREC. 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 Committees (MoDREC) are established by the 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.

National Research Ethics Advisers’ Panel

10. The National Research Ethics Advisers’ Panel (NREAP) is established by NRES under GAfREC as a resource to the UK Health Departments’ Research Ethics Service and the appointing authorities of RECs within that service, to help optimise research ethics review and so improve the research environment in the UK. The role of the NREAP includes advice to NRES on the development of operational policy, as well as advice and support to RECs and their appointing authorities in exercising their responsibilities under GAfREC and the SOPs. The full terms of reference for the panel are set out separately from this document.

Implementation

11. Subject to paragraph 11, version 5.0 of the NRES SOPs will come into effect on 1 September 2011 and applies retrospectively to all research already underway with a favourable opinion from a REC. Where the SOPs state that a particular procedure “should” be followed - without qualification - all RECs adopting the SOPs will be expected to comply fully. Compliance will be monitored through REC operational managers. The system of audit and accreditation of RECs developed by NRES is based on GAfREC and the SOPs.

12. The arrangements for electronic submission of applications from IRAS (see in particular paragraphs 1.32-1.39, 4.32 and 5.15 of these SOPs) will be brought into effect once the supporting IT and operational systems have been fully tested. Further details of implementation arrangements will be released on the NRES website.

References in this document to “health and social care” should be taken to mean “health and community care” in Scotland.
meantime, version 4.1 of the SOPs will continue to apply to booking and submission of applications, SSAs and substantial amendments.

13. The timing of implementation of Proportionate Review procedures will be determined by operational managers, taking into account the nature of research reviewed by RECs and operational considerations (see paragraph 8.14).

14. The procedures for collaboration and communication with ARSAC and NIGB (see paragraphs 13.50-13.111) will come into effect once as soon as agreements between NRES and these bodies have been formalised and, in the case of ARSAC, new functionality is ready within IRAS.

15. RECs may develop additional local operating procedures to deal with local matters not addressed in these SOPs or where discretion is permitted. Local operating procedures should be agreed between the Chair and the REC operational manager.

16. The standard letters and other documents listed in Annex A have been issued electronically to REC Co-ordinators for use alongside these SOPs, together with further operational guidance on use of the standard letter templates.

Terminology

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

- Responsibilities assigned in the SOPs to the “NRES Director” or the “NRES Head of Operations” may be delegated to another NRES member of staff.

- 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 officers 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 officers becomes available. When the Chair (or a vice-Chair) is in the chair, other officers resume their status as members.

- References to the REC Co-ordinator should be interpreted as referring also to an Assistant Co-ordinator or any other member of staff undertaking the duties of the Co-ordinator.

- The “main REC” means the REC undertaking the ethical review of an application or, in the case of research that is underway, the REC that gave a favourable opinion or its successor. In the case of research studies with ethical approvals from more than one REC prior to 1 March 2004, one of the RECs should be appointed as main REC to review amendments (see paragraph 10.10).

Further information

18. RECs requiring further information or advice should in the first instance contact their REC operational manager.
19. Researchers and other enquirers may seek advice by contacting queries@nres.nhs.uk or the appropriate REC Co-ordinator or operational manager.

March 2012

Health Research Authority
National Research Ethics Service
Skipton House
80 London Road
London SE1 6LH

http://www.nres.nhs.uk/

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**Terminology**

### Glossary

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<th>Term</th>
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<tr>
<td>Adverse Reaction</td>
<td>In a CTIMP, any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject. See also SSAR and SUSAR.</td>
</tr>
<tr>
<td>Amendment</td>
<td>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.</td>
</tr>
<tr>
<td>Appointing Authority</td>
<td>The body responsible for the establishment and support of REC.</td>
</tr>
<tr>
<td>Appeal</td>
<td>Following the issue of an unfavourable opinion, the submission of the application without revision to another REC for a second ethical opinion.</td>
</tr>
</tbody>
</table>
| 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 ethical opinion.  
*Note: Approval conditions are distinct from the further information or clarification requested from the applicant when issuing a provisional opinion.* |
| ARSAC                     | Administration of Radioactive Substances Advisory Committee.                                                                                                                                                |
| ASR                       | Annual safety report (see also DSUR).                                                                                                                                                                         |
| ATMP                      | Advanced therapy medicinal product – see Annex J.                                                                                                                                                           |
| Authorised REC            | A REC established under GAfREC but not recognised by UKECA. An authorised REC may review all applications except those relating to CTIMPs.                                                                  |
Booking

The booking of a new application or an appeal for review by a REC, and reservation of an agenda slot. Bookings may be made through CAS/LAS or direct to the office of a local REC, depending on the type of application.

Care organisation

The organisation(s) 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.

CAS

Central Allocation System, the booking system administered by NRES Head Office for certain types of application.

Chair

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

Chief Investigator (CI)

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

Clinical Trials Regulations

The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Clock

The period allowed for the ethical review of a new application or substantial amendment. 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 amendments, a 35 day clock applies in all cases and the clock does not stop.

COREC

The Central Office for Research Ethics Committees (COREC) was the predecessor of NRES.

CTA

Clinical Trial Authorisation, the authorisation from the MHRA to conduct a CTIMP. No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the REC may be made in parallel.
<table>
<thead>
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<th>Term</th>
<th>Definition</th>
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<tbody>
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<td>CTIMP</td>
<td>Clinical trial of an investigational medicinal product. (Any other type of research is known as a non-CTIMP.)</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Sciences, the Federal Government department responsible for regulations on health research in the United States.</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee (see guidance at <a href="http://www.nres.nhs.uk/applications/guidance/clinical-trials/?entryid62=74624">http://www.nres.nhs.uk/applications/guidance/clinical-trials/?entryid62=74624</a>)</td>
</tr>
<tr>
<td>Domain</td>
<td>The area covered by a SHA (England), a Health Board (Scotland), a regional office of the NHS Wales Department or the whole of Northern Ireland.</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report, the common format for annual safety reports on investigational drugs in the ICH regions under ICH guideline E2F.</td>
</tr>
<tr>
<td>Electronic signature</td>
<td>A digitally encrypted signature capable of verification by an independent service provider, in accordance with the Electronic Signatures Regulations 2002</td>
</tr>
<tr>
<td>Employing organisation</td>
<td>An organisation employing the Chief Investigator, other investigators or research collaborators. Employers remain liable for the work of their employees</td>
</tr>
<tr>
<td>EudraCT</td>
<td>The European Clinical Trials Database administered by the European Medicines Agency on behalf of the European Commission.</td>
</tr>
<tr>
<td>EVCTM</td>
<td>The Eudravigilance Clinical Trials Module of EudraCT.</td>
</tr>
<tr>
<td><strong>GAfREC</strong></td>
<td>The UK Health Departments’ Governance Arrangements for Research Ethics Committees.</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>GTAC</strong></td>
<td>Gene Therapy Advisory Committee. See paragraphs 1.18-1.21 and Annex J.</td>
</tr>
<tr>
<td><strong>HRA</strong></td>
<td>The Health Research Authority in England</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>IMP</strong></td>
<td>Investigational medicinal product.</td>
</tr>
<tr>
<td><strong>Investigator’s brochure</strong></td>
<td>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 subjects</td>
</tr>
<tr>
<td><strong>IRAS</strong></td>
<td>Integrated Research Application System, the on-line application system used to apply for most permissions and approvals for research in health and social care in the UK. See <a href="http://www/myresearchproject.org.uk">http://www/myresearchproject.org.uk</a>.</td>
</tr>
<tr>
<td><strong>LAS</strong></td>
<td>Local Allocation System, a telephone booking system for applications to a group of RECs supported from a single administrative centre.</td>
</tr>
<tr>
<td><strong>Lead site</strong></td>
<td>In the case of a multi-site study, the site for which the Chief Investigator is also the Principal Investigator.</td>
</tr>
<tr>
<td><strong>Local collaborator</strong></td>
<td>A person undertaking certain types of straightforward research procedure, not requiring the appointment of a Principal Investigator and a site-specific assessment (see “SSA-exemption”). Local collaborators at NHS sites should still seek approval from the R&amp;D office.</td>
</tr>
</tbody>
</table>
Main REC

The REC undertaking the ethical review of the application.

MHRA

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

Minor amendment

An amendment which is not a substantial amendment, not requiring review by a REC (see paragraph 5.34).

Modified amendment

Following the issue of an unfavourable opinion on a substantial amendment, the re-submission of the amendment in modified form.

MoDREC

The two Research Ethics Committees established by the Ministry of Defence to review research involving the British Armed Forces or otherwise sponsored or funded by the MoD. See paragraphs 1.29-1.31.

Non-CTIMP

Any research study that is not a CTIMP.

NRES

National Research Ethics Service, a division of the HRA in England.

NRES Director

The senior manager with overall responsibility for management of the National Research Ethics Service.

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.

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, participants in CTIMPs are referred to as “subjects”.)
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 subjects of the trial.

Principal Investigator (PI)
The investigator responsible for the research site where the study involves specified procedures requiring site-specific assessment (SSA). There should be one PI for each research site. In the case of a single-site 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.

Provisional opinion
A decision reached by a REC on an application, subject to the receipt of further information or clarification from the applicant (including revisions of documentation) and/or further consultation with a referee. The 60 day time period is suspended until information requested from the applicant is received.

PRS
Proportionate Review Service

REC
A Research Ethics Committee established in any part of the UK in accordance with GAfREC 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 operational manager
A generic term for the Research Ethics Service manager with first line responsibility for professional oversight and support of the REC office. The title of the postholder will vary, according to the type of REC and the context:

NRES RECs in England (including GTAC) – refer to the Addendum to the SOPs issued separately by the NRES Head
of Operations.

NHS RECs in Northern Ireland, Scotland or Wales - the Office for Research Ethics Committee Manager for the country concerned.

Social Care REC – the senior manager appointed by SCIE.

**RED**

The Research Ethics Database used by the REC system.

**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 ethical 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.

**Research site**

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

**Revision of application**

Any changes made to the terms of an application at the request of the REC following the meeting or, following issue of an opinion, before the research has started. Revision is not permitted prior to the REC meeting once the application has been validated.

**SAE**

Serious Adverse Event (see statutory definition on page 30).

**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.

**Second REC**

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

23
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ethical opinion</td>
<td>The ethical opinion given by a REC on a research study, with application to the whole of the UK. An ethical opinion may be either favourable or unfavourable.</td>
</tr>
<tr>
<td>Site-specific assessor</td>
<td>The body responsible for undertaking a site-specific assessment, either the R&amp;D office for a NHS site or an appropriate local REC for a non-NHS site.</td>
</tr>
<tr>
<td>Social Care REC</td>
<td>The national REC for review of adult social care research in England, appointed by SCIE. See paragraph 1.26 and Annex K.</td>
</tr>
<tr>
<td>SOPs</td>
<td>The Standard Operating Procedures issued by the NRES Head Office.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>See statutory definition on page 30.</td>
</tr>
<tr>
<td>SSA</td>
<td>Site-specific assessment, an assessment of the suitability of the investigator, site and facilities for each research site. SSA is undertaken for certain types of study only. See section 4 of the SOPs.</td>
</tr>
<tr>
<td>SSAR</td>
<td>Suspected Serious Adverse Reaction (see statutory definition on page 31).</td>
</tr>
<tr>
<td>SSI Form</td>
<td>Site-Specific Information Form</td>
</tr>
<tr>
<td>Substantial amendment</td>
<td>Under the Directive and the Clinical Trials Regulations, an amendment to a CTIMP that must be notified to both the ethics committee and the competent authority; it requires a favourable opinion from the main REC and/or a notice of no objection from the MHRA before it can be implemented. In the case of non-CTIMPs, a substantial amendment requires the issue of a favourable opinion from the main REC except where it only involves adding a new site or PI at a NHS site.</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction (see statutory definition on page 31).</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Transfer</td>
<td>The transfer of an application by the receiving REC to another REC for review.</td>
</tr>
<tr>
<td>UKECA</td>
<td>United Kingdom Ethics Committee Authority.</td>
</tr>
<tr>
<td>Validation</td>
<td>An administrative check carried out by a REC Co-ordinator to verify that an application is complete and may be accepted for review. Decisions on validation should be made within 5 working days of receipt.</td>
</tr>
<tr>
<td>Validation date</td>
<td>The date on which a valid application is received by a REC (see paragraph 1.42).</td>
</tr>
</tbody>
</table>
Statutory definitions relating to CTIMPs

Note: The following is a selection of relevant definitions from The Medicines for Human Use (Clinical Trials) Regulations 2004, relating to clinical trials of investigational medicinal products.

Authorised health professional

(a) a doctor
(b) a dentist
(c) a nurse
(d) a pharmacist.

Note: The Chief Investigator and any investigator (i.e. Principal Investigator) at a site in a CTIMP must be one of the above. See under “healthcare professional” for details of registration requirements.

Chief Investigator

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

(b) In relation to a clinical trial conducted at more than one trial site, the authorised health professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.

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

Clinical trial

Any investigation in human subjects, 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 subject 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.

**Healthcare professional**

A healthcare professional means any of the following:

<table>
<thead>
<tr>
<th>Profession</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>Registered medical practitioner</td>
</tr>
<tr>
<td>Dentist</td>
<td>Registered under the Dentists Act or entered in the list of visiting EEC practitioners under Schedule 4 to the Act</td>
</tr>
<tr>
<td>Nurse</td>
<td>Registered nurse or registered midwife</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>Registered pharmaceutical chemist under the Pharmacy Acts 1952 and 1954, or Articles 6 and 9 of the Pharmacy (Northern Ireland) Order 1976</td>
</tr>
<tr>
<td>Ophthalmic optician</td>
<td>Registered under section 7 of the Opticians Act 1989</td>
</tr>
<tr>
<td>Osteopath</td>
<td>As defined by section 41 of the Osteopaths Act 1993</td>
</tr>
<tr>
<td>Chiropractor</td>
<td>As defined by section 43 of the Chiropractors Act 1994</td>
</tr>
<tr>
<td>Other healthcare professionals</td>
<td>Registered by the Health Professions Council under the Health Professions Order 2001. This provides for registration of arts therapists, chiropodists, clinical scientists, dieticians, medical laboratory technicians, occupational therapists, orthoptists, paramedics, physiotherapists, practising psychologists, prosthetists and orthotists, radiographers, speech and language therapists.</td>
</tr>
</tbody>
</table>
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

The authorised health professional responsible for the conduct of a clinical trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the investigator is the leader responsible for that team.

Note: In the UK REC system, the term Principal Investigator will be used for the lead investigator at a site. There may be other local investigators at a site, 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 subjects.

Non-interventional trial

A study of one or more medicinal products which have a marketing authorisation, where 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.

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 subjects of the trial.

**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.

**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 amendments, modified amendments and the conclusion of the trial
(b) communications relating to urgent safety measures
(c) pharmacovigilance reporting.

**Substantial amendment to a clinical trial authorisation**

An amendment to the clinical trial authorisation which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects 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.

**Note:** The Clinical Trials Regulations define a substantial amendment in relation to the CTA rather than the terms of the REC application or the protocol. However, they provide that where the sponsor proposes to make a substantial amendment to a CTA which consists of, or includes, an amendment to the terms of the REC application or the supporting documentation, the amendment may be made only if the REC has given a favourable opinion.

**Suspected serious adverse reaction (SSAR)**

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

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Section 1: New applications for ethical review

Summary

New applications must be submitted by the Chief Investigator (CI) on the national REC application form within the Integrated Research Application System (IRAS). Only one application for ethical review should be made for any research study in the UK (except where review is required under both Mental Capacity Act and Adults with Incapacity (Scotland) Act).

Section 1 outlines the process for allocating applications to Research Ethics Committees (RECs), depending on the type of research.

The Clinical Trials Regulations require clinical trials of investigational medicinal products (CTIMPs) to be reviewed by RECs that are legally “recognised” by the United Kingdom Ethics Committee Authority (UKECA). There are two types of recognised committee for new applications:

Type 1: Phase 1 clinical trials in healthy volunteers taking place anywhere in the UK
Type 3: Clinical trials in patients taking place anywhere in the UK.

RECs that are not recognised by UKECA are referred to as “authorised” RECs and can generally review any research other than CTIMPs. RECs may be “flagged” for review of types of research where they have particular expertise. Application to a flagged REC is recommended but in most cases not mandatory.

Guidance is given on the remits of specialist RECs including the Gene Therapy Advisory Committee, Social Care REC and the Ministry of Defence RECs.

Operation of the REC system is facilitated by a Research Ethics Database (RED). All new applications are entered on RED and assigned a unique REC reference number. The database generates documentation such as standard letters (SLs), minutes and agenda.

The NRES Central Allocation System (CAS) is a telephone booking service, which allocates certain types of application, including all CTIMPs in patients, to RECs throughout the UK. Phase 1 CTIMPs in healthy volunteers are normally booked directly with a Type 1 recognised committee. Other applications are booked directly by phone with a Research Ethics Committee or Local Allocation System for the local REC centre. Applications are given a REC reference number and booked at a meeting for review.

Following implementation of electronic submission from IRAS, all applications and supporting documentation will be submitted electronically from IRAS at the time of booking. *(In the interim, previous SOPs apply under which a paper application must be sent within 4 days of booking, not including the day of booking, or 2 days in the case of a PRS application.)* The REC Co-ordinator then has 2 working days (applications submitted for proportionate review by sub-committee) or 5 working days (all other applications) to validate the application and notify the applicant. Section 1 defines the “validation date” and the criteria for a valid application.

Guidance is given on transferring applications. In some cases a REC is not permitted to review an application, and transfer to another REC is mandatory. Where the transfer is for operational reasons (e.g. a meeting is to be cancelled), the applicant is offered an optional transfer but may choose to wait for the next meeting of the first REC.

Guidance is given on the circumstances where a revised application form is required.

The remit of a REC is set out in GAfREC and includes current legal requirements for REC review. Section 1 advises when applications outside a REC’s normal remit may be accepted.
RECs only review projects considered to be research. Guidance is given on handling requests for advice on whether a project is research or some other type of activity. Applications submitted retrospectively should not be accepted for review.
**General requirements for submission of new applications**

1.1 An application for ethical review of a research study should be made by the Chief Investigator for that study. Applications may not be submitted by the sponsor(s) on behalf of the Chief Investigator. The Chief Investigator should normally be professionally based in the United Kingdom. For international studies with a coordinating investigator outside the UK, a health professional based in the UK should normally be nominated as the Chief Investigator 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 ethical review whether adequate arrangements are in place for supervision of the study in the UK.

1.2 Only one application for ethical 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 and Scotland – see paragraph 12.57). In the case of studies requiring site-specific assessment as part of the ethical review, the procedures in Section 4 apply. 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 ethical 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 ethical review to a Research Ethics Committee (REC) in the UK should be submitted on the standard on-line REC application form in the Integrated Research Application System (IRAS) ([http://www.myresearchproject.co.uk](http://www.myresearchproject.co.uk)). The standard application form may be revised from time to time by NRES Head Office. (See paragraph 1.45 for additional documentation required for a valid application.)

1.5 Applications should be booked for review prior to submission (see paragraph 1.32-1.39 for detailed booking procedures).

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**Allocation of new applications**

1.6 New applications for ethical review should be booked and allocated for review as 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 1.65-1.78.
Clinical trials of investigational medicinal products (CTIMPs)

<table>
<thead>
<tr>
<th>Type of CTIMP</th>
<th>Booking procedure</th>
<th>Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 trial in healthy volunteers (including patients without the target disease or condition – see paragraph 1.17)</td>
<td>Direct with REC office (or via LAS)</td>
<td>Type 1 recognised ethics committee</td>
</tr>
<tr>
<td>Advice on early agenda slots at all Type 1 recognised RECs may be sought from CAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1/2a trial in both healthy volunteers and patients with the target disease or condition</td>
<td>Via CAS</td>
<td>NHS REC with both Type 1 and Type 3 recognition</td>
</tr>
<tr>
<td>Trial of gene therapy</td>
<td>Direct with REC office</td>
<td>GTAC (but may be transferred to flagged NHS REC – see paragraphs 1.74-1.75)</td>
</tr>
<tr>
<td>Trial of stem cell therapy involving cells derived from stem cell lines</td>
<td>Direct with REC office</td>
<td>GTAC</td>
</tr>
<tr>
<td>Trial of other advanced therapy medicinal product (see paragraph 1.19)</td>
<td>Via CAS</td>
<td>Normally GTAC (but may be allocated to other appropriately recognised REC at request of applicant or if GTAC does not have available agenda slot)</td>
</tr>
<tr>
<td>All other trials in patients</td>
<td>Via CAS</td>
<td>Type 3 recognised NHS REC</td>
</tr>
</tbody>
</table>
### Other research

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Booking procedure</th>
<th>Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research involving prisoners or conducted within the prison services of the UK</td>
<td>Via CAS in England and Wales</td>
<td>Normally to flagged REC in England and Wales</td>
</tr>
<tr>
<td></td>
<td>Via LAS in Scotland and Northern Ireland</td>
<td>Any REC in Scotland or Northern Ireland</td>
</tr>
<tr>
<td>Research involving adults lacking capacity</td>
<td>Via CAS</td>
<td>See detailed guidance in Section 12</td>
</tr>
<tr>
<td>Research involving children</td>
<td>Via LAS</td>
<td>Normally to flagged REC</td>
</tr>
<tr>
<td>Research within the remit of the Social Care REC In England (see paragraph 1.26)</td>
<td>Direct with REC office</td>
<td>Social Care REC</td>
</tr>
<tr>
<td>Research involving patients at independent hospital / clinic / medical agency, nursing home or residential home in Northern Ireland</td>
<td>Via LAS in Northern Ireland</td>
<td>HSC REC with UKECA recognition</td>
</tr>
<tr>
<td>Research with funding from the US DHHS or one of its agencies (see paragraph 1.10)</td>
<td>Via CAS</td>
<td>Flaged REC for US DHHS-funded research</td>
</tr>
<tr>
<td>Research involving medical devices</td>
<td>Via CAS or LAS</td>
<td>Normally to flagged REC</td>
</tr>
<tr>
<td>Research tissue bank</td>
<td>Via CAS</td>
<td>Normally to flagged REC</td>
</tr>
</tbody>
</table>
Special 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 ethical 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 NRES Head of Operations, in consultation and agreement with the REC concerned and its operational manager, and approved by the NRES Management Group. The NRES Head of Operations 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. Lists of flagged RECs are available on the NRES website by using the advanced search tool under Find your Local REC on the Contacts page and are updated from time to time.

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

- Research involving children
- Research involving adults lacking capacity in England and Wales
- Research involving prisoners\(^4\) in England and Wales or otherwise conducted within the National Offender Management Service
- Research in the social care sector

\(^4\) A prisoner for this purpose means any person detained in the custody of HM Prison Service (i.e. within the National Offender Management 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.
- Research on medical devices
- Research involving stem cell therapy derived from stem cell lines, or other advanced therapy medicinal products
- First in human trials involving patients with the target disease or condition
- Low risk gene therapy CTIMPs transferred from GTAC to other RECs
- Research databases
- Research tissue banks.

1.10 In some instances, flagging of RECs is based on legal or regulatory authority for 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.

<table>
<thead>
<tr>
<th>Type of research</th>
<th>Geographical scope</th>
<th>Applicable REC(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial of an investigational medicinal product</td>
<td>UK-wide</td>
<td>REC with appropriate type of recognition from UKECA (see paragraph 1.17)</td>
</tr>
<tr>
<td>CTIMP for gene therapy</td>
<td>UK-wide</td>
<td>GTAC (see paragraph 1.18)</td>
</tr>
<tr>
<td>Non-CTIMP involving adults lacking capacity</td>
<td>Scotland</td>
<td>Scotland A REC (see paragraph 12.50)</td>
</tr>
<tr>
<td>Non-CTIMP involving adults lacking capacity</td>
<td>England and Wales</td>
<td>A REC in England or Wales</td>
</tr>
<tr>
<td>Research involving patients at independent hospital / clinic / medical agency,</td>
<td>Northern Ireland</td>
<td>REC with recognition from UKECA</td>
</tr>
<tr>
<td>nursing home or residential home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research funded by the US DHHS or one of its agencies</td>
<td>UK-wide</td>
<td>A REC with a current registration with the US DHHS’s Office for Human Research</td>
</tr>
</tbody>
</table>
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, it is mandatory for trials of stem cell therapy involving cells derived from stem cell lines to be submitted to GTAC.

1.13 In all other cases, review by a flagged REC is strongly recommended to applicants and will be the preferred allocation by CAS or LAS. However, allocation decisions may take into account other factors, including:
   - whether a timely agenda slot is available at a flagged REC
   - the geographical proximity of flagged RECs to the CI’s professional base (potentially affecting the CI’s ability to attend the REC meeting)
   - previous review of a closely related project by a non-flagged REC
   - any preference expressed by the CI for review by a particular REC (see paragraph 1.35)
   - the application may relate to more than one flagged area (e.g. prisons research involving adults lacking capacity) and it may not always be practicable to identify a REC with a dual flag.

1.14 Allocations to non-flagged RECs (or to a REC without another relevant flag for the application) should be agreed with the Co-ordinator of the REC concerned. Advice should be sought from operational managers where there is doubt about the appropriateness of a particular allocation.

1.15 Where a non-flagged REC is allocated an application that would normally be reviewed by a flagged REC, the Co-ordinator and the Chair should consider 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.

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 The terms of recognition for an ethics committee specify that it is recognised in one or more of the following categories:

Type 1 Committees recognised to review phase 1 CTIMPs taking place at any site in the United Kingdom, where the sponsor has no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial, and the subjects are healthy volunteers or patients not suffering from the disease or condition to which the trial relates.
Type 2 Committees recognised to review CTIMPs in patients (whether Phase 1 or later phase) taking place only at sites within the domain of the REC, i.e. an area defined by the geographical remit of the REC’s appointing authority. (Note: New applications are no longer allocated for review by RECs with Type 2 recognition. Such recognition is only relevant for active single domain trials for which Type 2 recognised RECs previously gave a favourable opinion and continue as the main REC.)

Type 3 Committees recognised to review CTIMPs in patients (whether Phase 1 or later phase) taking place at any site in the UK. (Note: RECs which are no longer recognised to review new applications for CTIMPs continue to be recognised by UKECA to act as main REC for trials of which they previously gave a favourable opinion, including review of substantial amendments, safety reports and any other associated work.)

Gene Therapy Advisory Committee

1.18 The Gene Therapy Advisory Committee (GTAC) is a NRES REC appointed by the Secretary of State for Health and is part of the UK Health Departments’ Research Ethics Service under GAfREC. GTAC has Type 1 and Type 3 recognition from UKECA. Under the Clinical Trials Regulations, any gene therapy CTIMP must be submitted to GTAC (though low risk gene therapy trials may be transferred to other RECs under the procedures in Annex J.).

1.19 In addition to its legal responsibility for trials of gene therapy medicinal products, GTAC is the national flagged REC for the following types of research:

- Trials of other Advanced Therapy Medicinal Products (ATMPs), i.e. somatic cell therapy and tissue engineered products
- Trials of stem cell therapy involving cells derived from stem cell lines
- Trials of vaccines involving recombinant vectors or vectors with potentially immuno-regulatory mediator molecules
- First in human trials of vaccine vectors (or variants of vectors in use) or of engineered antigen molecules
- Other non-CTIMP gene therapy research (e.g. non-interventional trials).

1.20 Research studies involving well-established adult stem cell therapies (for example, bone marrow transplantation) or types of vaccine may be reviewed by any appropriate REC.

1.21 Detailed guidance on the remit of GTAC is at Annex J. Any queries about the allocation of particular studies should be referred to the GTAC Co-ordinator.

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[Note: paragraphs 1.22-1.23 were deleted by Amendment No. 1 to Version 5.0]

Non-interventional trials of medicinal products
1.24 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**

1.25 The MHRA has published guidance on the interpretation of the statutory definition of a CTIMP and a non-interventional trial (see algorithm at Annex B). 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 if necessary – see paragraph 13.10.) The REC should proceed with the ethical review but advise the applicant of the possible consequences if the application has been wrongly classified. The applicant may be required to provide written evidence from the MHRA as part of the single request for further information (see Section 3). Where the MHRA advises that an application submitted as a non-CTIMP is in fact a CTIMP, the application should be withdrawn and re-submitted with a EudraCT number and the additional information required. 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 paragraph 5.3 of Annex D.

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**Social Care Research Ethics Committee**

1.26 The Social Care Research Ethics Committee is a NRES REC appointed by the Social Care Institute of Excellence (SCIE) and part of the UK Health Departments’ Research Ethics Service under GAfREC. It is recognised as an appropriate body for the purpose of the Mental Capacity Act 2005. The Social Care REC reviews the following types of applications submitted by researchers based in England:

(a) adult social care research
(b) other studies using social sciences methodology and not involving any clinical interventions or changes to clinical care.

1.27 The remit of the Social Care REC is described in more detail in Annex K. Where research falls within this remit, researchers are strongly encouraged to apply directly to the Social Care REC. Queries about the appropriate source of review for studies in adult social care in England (including cross-border studies) should be referred to the Social Care REC Co-ordinator for advice.

1.28 Research involving NHS patients and, subject to paragraph 1.90, NHS staff may be accepted for review by the Social Care REC where it uses social science

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5 Social care research in Wales and Northern Ireland is reviewed by RECs in those countries. The Social Care REC may review social care research taking place in England and another UK country. Where the project involves adults lacking capacity in Scotland as well as England/Wales, separate review is required by the Scotland A REC (see paragraph 12.59).
methodology and does not involve any clinical interventions or changes in clinical practice. Guidance should be sought from the Social Care REC Co-ordinator on a case by case basis. Where such applications are accepted for review, they do not then require separate review by another REC.

Ministry of Defence Research Ethics Committees (MoDREC)

1.29 The Ministry of Defence appoints two Research Ethics Committees to undertake ethical review of research involving the UK Armed Forces or otherwise sponsored or funded by the MoD:

- Ministry of Defence Research Ethics Committee (General)
- Ministry of Defence Research Ethics Committee (Personnel, Protection and Effectiveness).

These RECs are known jointly as MoDREC. They are not part of the UK Health Departments’ Research Ethics Service but operate to standards set out by the MoD which are compatible with those in GAfREC and these SOPs. MoDREC is recognised by UKECA to review CTIMPs involving subjects who are UK Armed Forces personnel recruited in a military setting, as well as Phase 1 trials in healthy volunteers conducted by the MoD or its agencies or contractors. 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.

1.30 Research within the remit of MoDREC should be submitted to MoDREC for ethical 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 NRES website at:

http://www.nres.nhs.uk/applications/approval-requirements/ethical-review-requirements/

1.31 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 ethical review by another REC unless review is required under the Adults with Incapacity (Scotland) Act 2000 (see paragraph 12.49).

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Procedures for booking and submitting applications

1.32 An applicant intending to submit a new application should first contact either the REC office, LAS or CAS, as appropriate, in order to:

- Seek advice on the correct allocation of the application

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6 See paragraph 11 of the Introduction to the SOPs in relation to implementation of arrangements for electronic submission.
• Seek advice on whether the study is suitable for review through the Proportionate Review Service where applicable, taking into account the criteria published on the NRES website (see paragraph 8.15)

• Book an agenda slot at the next full meeting of an appropriate REC (or with a sub-committee for proportionate review)

• Obtain a REC reference number for the application.

1.33 When giving advice, the REC Co-ordinator or LAS/CAS Co-ordinator (“booking Co-ordinator”) should use the appropriate booking checklist issued by the NRES Head of Operations.

1.34 Applicants should be offered the first available meeting slot at an appropriate REC (either a full meeting or a sub-committee for proportionate review, as appropriate). If the applicant agrees, the application should be assigned to this meeting.

1.35 The applicant may decline the first available slot if he/she has a preference for a particular REC that is either geographically convenient or has prior knowledge of closely related research (for example, it has reviewed an earlier phase trial of the same medicinal product). LAS/CAS should check that the preferred REC is recognised to review the application. If so, the application should be assigned to the next meeting of this REC. If its next agenda is full, the applicant should be advised of the opportunity to book with another REC that is able to offer an earlier meeting slot. In the case of LAS bookings, where no slots are available locally within the next 3 weeks, neighbouring centres should be contacted to identify slots at their RECs which may be offered to the applicant. The applicant may however decline the alternatives offered to them and opt to wait for the next meeting of their preferred REC with an available slot. In this case, the validation date is deferred until the closing date for applications to the preferred REC (see paragraph 1.42). Applications should not be booked any further ahead than this in order to reserve slots.

1.36 Once a suitable agenda slot has been agreed with the applicant, the booking Co-ordinator should check that the applicant is ready to submit the application and all supporting documentation from IRAS before accepting the booking. Once the booking has been accepted, the application form and supporting documentation will be uploaded electronically from IRAS to the Research Ethics Database (RED). The booking Co-ordinator should send confirmation of the booking to the applicant by email. In the case of bookings made by LAS/CAS, the Co-ordinator of the REC to which the application has been allocated should also be notified by email.

1.37 If the applicant is not ready to submit the application including all required authorisations and supporting documentation, the booking should not be accepted. The applicant should be advised to re-book once the application is complete and ready for submission.

1.38 Applications should not normally be accepted unless booked and submitted electronically from IRAS. In exceptional circumstances, Co-ordinators have discretion to accept submission of the application form and/or supporting documentation in another electronic format (e.g. by email or on CD) where the applicant is unable to submit from IRAS due to technical problems with IRAS or RED and the submission is urgent. Where possible, the applicant should arrange for any
necessary declarations to be signed and scanned to PDF, but the Co-ordinator has discretion to accept the application without signatures. Once full IRAS/RED functionality is available, the applicant should still submit the application form from IRAS as soon as possible so that relevant data can be uploaded into RED.

1.39 Paper applications should not be accepted in any circumstances.

Validation of applications

The validation date

1.40 The relevant period, within which an ethical opinion must be given (see paragraphs 3.1-3.2), begins when a valid application is received by any REC.

1.41 Subject to paragraph 1.42, the relevant date (“the validation date”) is the working day on which the complete application is received electronically in RED by the REC, including all relevant authorisations and all supporting documents.

1.42 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

1.43 It is normally the responsibility of the receiving REC Co-ordinator to decide whether or not the application is valid and to notify the applicant. Notification should normally be given within 5 working days of receiving the application, or within 2 working days for applications submitted for proportionate review. Where an application is transferred to another REC, responsibility for validation passes to the Co-ordinator for the REC to which the application is transferred (see paragraphs 1.73-1.75).

1.44 The Co-ordinator should use the appropriate validation checklist issued by the NRES Head of Operations. Further advice may be sought from the REC operational manager where necessary. The agreement of the Chair is not required.

Validation criteria

1.45 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 electronically from IRAS to RED together with all supporting documents. (The checklist in IRAS indicates which documents are mandatory.)

(b) Parts A, C and D of the standard application form have been submitted, together with relevant sections of Part B where applicable. (In some cases the SSI form may also be submitted initially – see paragraph 1.47).

(c) All relevant sections and questions in the application form have been completed (see paragraph 1.48), the text is in English and the print is clearly legible.

(d) The application form has been electronically authorised in IRAS by the Chief Investigator and the authorised representative of the lead sponsor (all applications); by the lead Medical Physics Expert and lead Clinical Radiation Expert (research involving the use of ionising radiation); and by the academic supervisor (applications submitted by students).

(e) Short curriculum vitae (a maximum of two pages is recommended) have been submitted for the Chief Investigator and, in the case of student applications, for both the student and academic supervisor.

(f) A research protocol, or an equivalent document such as a project proposal, has been submitted. The protocol should be complete; it is not acceptable to submit amendments alongside the protocol except as permitted by paragraph 5.11.

(g) Supporting documents have been 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 lead sponsor for the purpose of correspondence on the REC application.

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7 Or exceptionally in another electronic format – see paragraph 1.38.

8 In the case of a CTIMP, the Clinical Trials Regulations allow for applications to be signed by the Chief Investigator by means of an “electronic signature” as defined in the Electronic Signatures Regulations 2002 (see Glossary). Systems for accepting this type of signature are not currently available. However, electronic authorisation of the application in IRAS is considered to satisfy the requirement of the Clinical Trials Regulations for a signed application.

9 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. Exceptionally it could be the CI or another member of the investigational team. If any doubt arises whether the person signing the declaration has been duly authorised, the Co-ordinator may request evidence, e.g. a letter from the sponsor, or check with the sponsor directly.
(i) Evidence\textsuperscript{10} has been provided, in the case of trials with a sponsor(s) or Chief Investigator outside the NHS, that the sponsor(s) and Chief Investigator have insurance or indemnity to cover any potential liability arising from the research (see Annex G). (In the case of research sponsored by a NHS body or with a Chief Investigator who is employed by the NHS, NHS indemnity will be ensured when final management permission is given for the research.)

(j) In the case of a CTIMP, the European Clinical Trials Database (EudraCT) number has been entered on the application form.

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

(l) In the case of a non-CTIMP, either the sponsor or the sponsor's legal representative is established within the UK.

(m) 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.

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

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

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

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

1.47 An SSI form may also be submitted if the study requires site-specific assessment (SSA) and is to be conducted at a non-NHS site for which the main REC is also the designated REC for SSA. In such cases, the main REC should carry out the SSA for this site alongside the ethical review.

1.48 It is essential that Part A of the application form is completed in full. Where further details are requested if a particular box is ticked, these must be provided. In particular, where the applicant indicates that referees' or other scientific critique reports are not enclosed, he/she must justify this and describe the process of scientific review. If there is no evidence to show that scientific review has taken place prior to submission, the application may be considered invalid. In the case of

\textsuperscript{10} The initial application should normally include supporting evidence in the form of an insurance certificate or documentation confirming that indemnity is in place, e.g. a letter from a medical defence society. However, Co-ordinators have discretion to validate applications without supporting evidence provided that the application form includes a clear statement about how cover will be arranged and the applicant undertakes to provide further evidence during the review or before the study starts (as a condition of a favourable opinion).
research undertaken mainly for educational purposes, review by the academic supervisor is considered appropriate.

1.49 Evidence from care organisations of their agreement in principle to the conduct of the research is highly desirable and should be encouraged, particularly for single-site research, but is not a criterion for validation except where the care organisation is the sponsor (see 1.45(d)). The process for securing final research governance approval to proceed with the research from care organisations and/or employing organisations is separate to the process of ethical review.

1.50 Although not a formal validation criterion, it is also highly desirable that applicants provide evidence in writing that project funding has already been obtained. This is particularly important for studies that are not commercially sponsored and require significant financial support from non-NHS bodies. If the ethics application has already been made, and the funding body requires changes to the protocol, it could be necessary to submit substantial amendments or even to withdraw and re-submit the application. Co-ordinators should offer guidance to applicants about this where appropriate.

Validation letters

1.51 If an application is valid, the REC Co-ordinator should notify the Chief Investigator using one of the following letters:

SL1 Validation of study requiring SSA (review at a full meeting)
SL2 Validation of study not requiring SSA (review at a full meeting)
SL2 (PR) Validation of study not requiring SSA (proportionate review).

1.52 A copy of the validation letter should be sent to the sponsor of the research. 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.

1.53 Co-ordinators should also send a copy of the validation letter to the lead NHS R&D office for any research to be conducted within the NHS.

1.54 The validation letter includes an invitation to the Chief Investigator to attend the REC meeting (see paragraphs 2.25-2.30). The Co-ordinator should insert details of the arrangements for the meeting, including any specific information about local meeting procedures. It may be helpful to enclose a list of members, including professional background and any specific areas of interest.

Invalid applications

1.55 In the case of an invalid application, the REC Co-ordinator should notify the Chief Investigator of the reasons why using SL3. The application is void and should be
deleted from the agenda for the next meeting. LAS/CAS should be notified that the agenda slot remains available. The Chief Investigator may re-book and re-submit the application, in which case it should be treated as a new application. The Co-ordinator should re-enter the application on RED and allocate a new REC reference number. The relevant day time period for review of the application does not start until a valid application is received.

1.56 Where an application is invalid but the outstanding information or documentation appears relatively straightforward, Co-ordinators may be able to follow this up with the applicant informally without needing to issue SL3. Where this occurs, the validation date is the date on which the last part of the information required for a valid application is received electronically by the REC office.

Validation of applications for proportionate review

1.57 For research studies in certain categories, the REC application form in IRAS invites applicants to consider whether they wish to have the study reviewed through the Proportionate Review Service (see section 8), taking into account the criteria published on the NRES website. Where an applicant selects the PRS option, it will be provisionally assigned for proportionate review by sub-committee on booking.

1.58 On receipt of an application assigned for proportionate review, the Co-ordinator should check the study’s suitability for review against the current criteria (see paragraph 8.15) 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 from the operational manager where necessary.

1.59 If the application is valid and suitable for proportionate review, SL2(PR) should be sent and the application should proceed to review by sub-committee under the procedures in Section 6.

1.60 If the application is valid, but unsuitable for proportionate review, the Co-ordinator should notify the applicant by telephone or email and explain the reasons. The application should be re-booked to a full REC meeting in discussion with the applicant and taking account of their preferences in the normal way. SL1 or SL2 should be sent as applicable.

1.61 If the application is invalid, the normal procedures under paragraphs 1.55-1.56 apply.

1.62 Where the application form indicates that the applicant does not wish to have the study reviewed through the PRS, but the Co-ordinator considers that it meets the criteria and no significant ethical issues have been presented warranting review by full committee, it may be re-assigned to a sub-committee for proportionate review. SL2(PR) should be sent, including additional explanation of why the application has been re-assigned.

Applications validated in error

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1.63 Where an application has been validated in error, the Co-ordinator should make every effort 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 ethical 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. If, however, the issues are fundamental, the application may need to be withdrawn or rejected.

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Transfer of applications to another REC

Mandatory transfer

1.64 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 1.10)

(b) One of the members or deputy members of the receiving REC is named in Part A of the application as the Chief Investigator or another key investigator/collaborator in the research. (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 2.57-2.61.)

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Optional transfer

1.65 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 due to 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 or deputy members of the receiving REC is deemed to have a significant potential conflict of interest in relation to the application.

1.66 Optional transfers under (a) in paragraph 1.65 should normally take place only after consultation with the Chief Investigator by phone or e-mail, and with his/her 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.

1.67 Although transfers under paragraph 1.65(a) should normally be with the Chief Investigator’s agreement, the REC Co-ordinator may proceed with the transfer with the approval of the REC operational manager if the Chief Investigator cannot be contacted.

1.68 An optional transfer under paragraph 1.65(b) should take place only after consultation with the REC operational manager and with his/her agreement.

1.69 In the case of optional transfers under paragraph 1.65(b) or (c), the validation date remains the date on which it was first received by the REC that transfers the application.

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Re-allocation of transferred applications

1.70 Where a transfer is to take place, the Co-ordinator of the receiving REC should notify the applicant by phone or e-mail, explaining why the REC is unable to review the application. Where it is possible to re-allocate within the same REC centre, the Co-ordinator should make the necessary arrangements in consultation with the applicant. Otherwise, the applicant should be advised of the arrangements required for re-allocation, either via CAS (if the application was booked initially through CAS) or through the LAS at another REC centre.

1.71 The Co-ordinator should seek advice from the REC operational manager on the re-allocation of applications requiring special expertise not available to the receiving REC.

1.72 Once the new allocation has been confirmed on RED, the electronic version of the application form will automatically be transferred to the second REC.

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Responsibility for validating transferred applications

1.73 Responsibility for validating a transferred application passes to the Co-ordinator of the second REC.

1.74 The Co-ordinator of 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 centre, 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.

1.75 It is recommended that, wherever possible, the Co-ordinator of 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 may be notified using SL3 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 Co-ordinator of the receiving REC may pass on this advice by phone or e-mail to the Co-ordinator of the second REC. This will enable the second Co-ordinator to issue the validation letter as soon as the documentation is received.

Transfers from the Gene Therapy Advisory Committee to other RECs

1.76 Procedures for transfer of low risk gene therapy applications from GTAC to other flagged RECs are set out in Annex J.

Revision of applications following submission

1.78 In general, revisions should not be accepted, prior to the REC meeting, to an application that has been validated and booked for review.

1.79 If the applicant considers it necessary to make significant revisions to the application form or the supporting documentation prior to review by the REC, he/she should withdraw the application (see paragraph 1.88). Any minor revisions may either be discussed at the meeting or dealt with later in accordance with paragraph 1.81.

1.80 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 ethical 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). 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 Notice of Substantial Amendment is submitted during the review process (see paragraph 5.11), it should be reviewed by the Chair/vice-chair and at least one other member.
1.81 If the Chair considers the proposed revisions to be both ethically significant and unrelated to the matters raised by the REC in the ethical 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.

1.82 When considering revisions to applications for multi-site studies requiring SSA, the main REC should also note the guidance in paragraph 4.66.

1.83 For revisions made after a favourable opinion has been given, refer to the procedures for review of amendments in Section 5.

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Submission of revised application forms

1.84 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.

1.85 It is also appropriate for REC offices 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 Notice of Substantial Amendment requires submission of a new or revised section of the form for review (see paragraphs 5.26 and 12.63);

(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;

(d) Where the CI or sponsor wishes to provide a revised version of the research summary for upload into RED and publication on the NRES website.

In the case of (c) and (d), revised forms are submitted for information; there is no need for the form to be re-reviewed or approved by the REC.

1.86 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 its provisional opinion, applicants should provide any additional information, clarification or correction by letter.

1.87 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 amendments 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 amendment requiring ethical review, they should be notified to the REC using the appropriate Notice of Substantial Amendment form. There is no need for the initial application form to be re-submitted.
Withdrawal of applications

1.88 If an applicant withdraws an application at any time, it should be treated as no longer valid and recorded as withdrawn in RED. Letter SL26 should be sent to the applicant. If the applicant wishes to re-submit the application, it should be re-booked with the REC or through LAS/CAS, as appropriate. A new REC reference number should be issued. A new clock commences when the valid application is re-submitted.

Research not requiring review by a REC

1.89 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 section 2.3 of GAfREC (including current legal requirements), the following procedures apply.

1.90 Research involving 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 2.3.14 - 2.3.16 of GAfREC) 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 the REC operational manager. Where a researcher or research sponsor wishes to apply to a REC, they are encouraged to seek advice in writing from the operational manager prior to completing an application.

1.91 Under paragraph 2.3.7 of GAfREC, RECs may agree to consider applications in respect of activities preparatory to research. 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. The application should normally be accepted under the procedures in Sections 11 and 15. If a REC feels unable to review the application, the Co-ordinator should make arrangements to transfer it to a REC willing to review it. Requests for review of pre-trial advertising and screening of healthy volunteers at clinical trial units may also be accepted by the usual SSA REC for the unit under the procedures in paragraph 4.55.

1.92 Paragraph 2.3.7 of GAfREC also allows a REC to review other research not requiring review under the policy and legal requirements set out in GAfREC. 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 ethical review from another source, e.g. a university REC or an ethics committee established by a professional body, the REC is encouraged to accept the application and give an ethical opinion on a voluntary basis. It is a matter for the Chair 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 Chair agrees to review the application, it should be reviewed in accordance with standard operating procedures. In responding to the applicant following the meeting, SL25 should be used. Where the Chair declines to review the application, the REC
operational manager should decide whether or not to invite another REC to consider the application.

**Advice on whether a project is research**

1.93 Under paragraph 2.3.13 of GAfREC, RECs are not expected to consider applications in respect of activities that are not research.

1.94 Within the NHS and social care services, the responsibility for determining whether a project should be managed as research under the Research Governance Framework lies with the responsible R&D office. 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 R&D office may itself seek further advice from a REC or the NRES Queries Line, or recommend that the sponsor or project team seeks such advice, by submitting a brief outline of the project in writing. Where a REC receives such a request, it should be referred to the Chair, who is encouraged to provide advice but is not obliged to do so. Where the Chair is available and willing to advise, a response should be sent within 5 working days using SL24. Otherwise, the correspondent should be referred to the NRES Queries Line.

1.95 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 GAfREC. 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 that the REC that the application is no longer considered to be research, the application and opinion letter should be considered to be withdrawn.

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**Retrospective applications**

1.96 In some cases, applicants may disclose that the research has already started without first obtaining a favourable ethical 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 REC operational manager, the NRES Head of Operations and the REC’s appointing authority in accordance with the procedures in paragraphs 9.98-9.101.

1.97 Such applications should be considered invalid, and the REC is not obliged to proceed with any form of ethical review. An ethical 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 ethical 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.
1.98 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.

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Section 2: Full meetings of a Research Ethics Committee

Summary
Applications not suitable for proportionate review by a sub-committee are reviewed at a full meeting of a REC. RECs normally meet monthly. There must be at least 10 scheduled full meetings each year for review of applications.

Meeting schedules and closing dates for applications are agreed with the responsible operational manager and publicised to NHS organisations and research bodies.

The Co-ordinator arranges distribution of agenda, applications and other papers for meetings in accordance with local procedures. The aim is for a REC to review around 6 applications at each meeting, and no more than 8. The Co-ordinator notifies members in writing of business conducted outside the meeting and circulate copies of sub-committee minutes.

Under the Clinical Trials Regulations a quorum must be present when giving an opinion on a new application. A record of attendance should be kept. A quorum is 7 members including the Chair or a vice-chair, one lay and one expert member. Deputy members may attend in place of an expert member. A maximum of two former members or members of other ethics committees may be co-opted at each meeting. Attendance of observers is at the REC’s discretion and subject to a confidentiality agreement.

Members must declare any material interests they have in relation to a study, either at or before the meeting. A REC cannot review a new application on which one of its own members or deputy members is named as an investigator. The Committee has discretion in dealing with other declared interests. Guidance is given on possible courses of action.

The Chief Investigator is invited to the meeting to respond directly to any comments or questions raised by the committee. Attendance is not compulsory, however, and if an investigator is unable to attend this should not prejudice the decision of the committee. The sponsor’s representative is also welcome to attend. Consideration should be given to inviting supervisors of student researchers.

Members who are unable to attend may send written comments prior to the meeting. Exceptionally, members may attend by teleconference or video-conference.

Committees usually appoint a lead reviewer(s) for each application to review it in greater detail and lead the discussion at the meeting. Lead reviewers receive a copy of the full protocol for the study as well as other papers.

RECs may seek the advice of a specialist referee, and this may be required when reviewing CTIMPs involving minors or adults lacking capacity. The REC can ask for written advice before or after the meeting, or invite the referee to the meeting.

The meeting is chaired either by the Chair, or if s/he is not available the vice-chair or alternate vice-chair. All members must be given appropriate opportunity to express their opinion and the meeting should attempt to reach a unanimous decision.

Guidance is given to Co-ordinators on the content of minutes. The minutes should be ratified by the REC at the next meeting. The ethical opinion given on each application should be made public in the REC’s annual report.
General policy

2.1 All valid applications for an ethical opinion should be reviewed at a full meeting of a REC held in accordance with the following procedures, except where the expedited or proportionate review procedures described in Section 8 apply.

2.2 Procedures relating to the outcome of the ethical 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 ethical review of applications. Additional meetings may be held where necessary to ensure that an ethical 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 at any time exceed two months.

2.5 REC operational managers should ensure that the meeting schedules of RECs in their areas are appropriately staggered, in particular over the holiday periods, to ensure that it is possible for any valid application to be reviewed within the relevant time limit.

2.6 The schedule of Committee meetings for the year commencing on 1 April should be agreed between the Co-ordinator and the REC operational manager by 30 September in the previous year. The schedule should set out the dates, times and venues of meetings, and the closing date for applications to each meeting. All members and deputy members of the REC should be issued with details of the schedule.

2.7 The closing dates for applications should normally be 14 calendar days prior to each REC meeting. Exceptionally, where the timeline for review under the Clinical Trials Regulations is 90 days or longer (see paragraph 3.2), the REC may set an earlier closing date for the application.

2.8 Following approval by the REC operational manager, REC Co-ordinators should arrange for their meeting schedules to be widely publicised to NHS organisations and other research bodies based in the area covered by the REC. The information publicised should include at least the dates of REC meetings and the closing dates for receipt of applications. Any changes made to the meeting schedule during the year should be similarly publicised. There is no requirement to publicise arrangements for sub-committee meetings.

2.9 The Co-ordinators of recognised RECs should also notify the REC operational manager and CAS of their meeting schedule for the forthcoming year and any
changes made during the year. Operational managers may request changes to meeting schedules to ensure that the system as a whole has sufficient operational capacity at all times.

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Agenda

2.10 The REC Co-ordinator should prepare the agenda for the meeting. A standard format is available in RED for optional use. The agenda should include at least the following:

- The date, time and venue of the meeting
- Declarations of interest relating to items on the agenda
- 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 ethical review to be considered at the meeting
- Lead reviewers for each application where applicable (see paragraphs 2.21-2.22)
- Report by the Co-ordinator (see paragraphs 2.15-2.20).

2.11 The agenda may also include discussion of the following where appropriate:

- General ethical 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.

2.12 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 ethical review. The aim of the Research Ethics Service is that RECs should review around 6 new applications per meeting on average, and no more than 8 at any meeting. The local operating limits should be agreed with the REC operational manager, taking into account the nature of the applications reviewed by the REC and the current demand for agenda slots. Operational managers will review the workload of RECs periodically.

2.13 Section 6 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, in particular where the Chair considers it important that a wider discussion takes place. In allocating business between the Committee and sub-committee meetings, the Co-ordinator and the Chair should weigh carefully the requirement to give ethical opinions within statutory time limits, the need to conduct REC business both efficiently and with due care, and the overall demands of the agenda on members.
Report by the Co-ordinator

2.14 Members should be notified in writing of business undertaken outside REC meetings, including at least the following:

- Decisions or actions taken by Committee officers or members under delegated authority (see paragraph 2.17)
- Decisions taken by a sub-committee either at a meeting or in correspondence (the minutes of any sub-committee meetings may be appended to the Co-ordinator’s report or copied to members separately)
- Progress reports on research with a favourable opinion (see paragraph 9.11)
- Receipt of annual safety reports on CTIMPs, and reports of Data Monitoring Committees (see paragraphs 9.37 and 9.62)
- Notification of the conclusion or early termination of research (see paragraph 9.79)
- Receipt of final study reports (see paragraph 9.104).

2.15 The Co-ordinator should prepare a report for distribution to members with the papers for each meeting, using the template in RED.

2.16 Where the REC has previously delegated authority to the Chair or a sub-committee to issue its opinion following receipt of further information or clarification from the applicant (see paragraphs 3.35-3.39), it should be notified once the opinion has been issued. The following information should be provided in the report:

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

2.17 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.

2.18 The Co-ordinator’s report should normally be distributed with the main papers for the meeting, but may be circulated nearer to the date of 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 Co-ordinator considers it essential that a matter is reported to the REC as soon as possible, a further written report may be prepared or an oral report made to the meeting.

2.19 The Co-ordinator’s report is mainly for the information of members and should not normally require detailed discussion. The decisions taken by Committee officers or members on behalf of the REC, or by sub-committees, 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, or about information received on the progress or
safety of research. Any such concerns should be considered by the REC and recorded in the minutes.

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Lead reviewers

2.20 RECs are encouraged to appoint one or more members as lead reviewers for each application. Where this is the local practice, the Co-ordinator should appoint suitable lead reviewers in discussion with the Chair and members as appropriate.

2.21 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.

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Distribution of papers for meetings

2.22 The REC Co-ordinator should arrange for distribution of the papers for the meeting 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. Papers 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. The local requirements for distribution of papers should be discussed and agreed by the REC. Papers may be distributed electronically to particular members with their agreement.

2.23 All members should receive and review the application form and all supporting documentation for each new application, except that RECs have discretion as follows:

- The protocol for the study should be sent at least to the lead reviewer(s) and to members with relevant expertise. Other members should be provided with a copy if they request it.
- The Investigator Brochure for an investigational medicinal product should be sent at least to members with relevant expertise (in particular, to the pharmacist or clinical pharmacologist).

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Attendance of the Chief Investigator and sponsor

2.24 The Chief Investigator should be invited to attend the meeting at which his/her application is to be reviewed. 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, many 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.

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

2.26 The REC may offer the Chief Investigator the alternative of being available by phone, tele-conference or video-conference at the time of the review. Wherever possible, speakerphone facilities should be arranged so that all members present in the room may question the Chief Investigator and hear the responses, and to enable the Co-ordinator to take full minutes. If this is not possible, the Chair or lead reviewer may hold a phone conversation with the CI and repeat their responses to the rest of the Committee.

2.27 In the case of applications submitted by students, the REC should consider inviting the academic supervisor to attend. In addition, where the student is conducting the research under supervision within the NHS or social care services, the professional supervisor may be invited to attend.

2.28 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.

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Quorum requirements and meeting attendance

2.29 Subject to paragraph 2.31, the quorum for meetings of a REC is seven members, including at least the following:

- The Chair or, if unavailable, the vice-Chair or alternate vice-Chair
- One lay member (either a “lay” or “lay+” member as defined in the NRES guidance)\(^{11}\)
- One expert member.

2.30 Members are normally expected to attend in person. However, in exceptional circumstances members may attend by teleconference or videoconference with the permission of the operational manager.

\(^{11}\) The definition of expert and lay members is defined in the Clinical Trials Regulations. Detailed guidance is given in the paper “Membership of recognised RECs”, available on the NRES website.
2.31 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 flagged RECs (see paragraph 1.10).

2.32 A deputy member who is attending in place of their “lead” member should be counted for the purpose of the quorum.

2.33 A co-opted member (see paragraphs 2.40-2.42) should also be counted for the purpose of the quorum.

2.34 The following should not be counted for the purpose of the quorum:
- The REC Co-ordinator or Assistant Co-ordinator
- 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 either in person or by teleconference or videoconference (see paragraph 2.44)
- Deputy members attending alongside the lead member.

2.35 Where a quorum is not present, the Committee may not give an opinion on any new application for ethical 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 applications will need to be re-booked for further review at a quorate meeting of the REC or transferred to another REC. The clock does not stop.

2.36 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 as if it were a sub-committee meeting, provided that the Chair (or vice-Chair or alternate vice-Chair) and at least one other member is present.

2.37 The Co-ordinator should keep a record of attendance, indicating which members and deputy members were present for the discussion of each application for ethical review.

2.38 Where the Co-ordinator of a REC is concerned that a forthcoming meeting may not be attended by a quorum of members due to foreseen absences, he/she should consider the following options with the REC operational manager:
- Co-opting up to two additional members (see paragraphs 2.40-2.41)
- Postponing and re-arranging the meeting
- Cancelling the meeting - where it is proposed to cancel a planned meeting, the agreement of the REC operational manager must be sought at an early stage.

2.39 If the meeting is postponed or cancelled, the Co-ordinator should consider with the REC operational manager the need 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

2.40 A REC may co-opt up to two additional members at any meeting of the REC for the purposes of that meeting. Except in the case of co-opting to GTAC, a person may be co-opted as a member only if he/she is or has been a member of another REC within the UK Health Departments’ Research Ethics Service or a member of MoDREC. Exceptionally, more than two members may be co-opted with the agreement of the operational manager provided that the meeting will not review any CTIMP applications. Deputy members may not act as co-opted members at their own REC, but may be co-opted by another REC if they have previously been a member of a REC as defined above.

2.41 Local procedures for co-opting members are the responsibility of the REC’s appointing authority, acting on advice from the REC operational manager and in accordance with guidance issued by the NRES Head of Operations. The manager should maintain records of members within the area who would in principle be willing to be co-opted where required. These could either be serving members, or ex-members appointed to a bank for a period of up to two years at a time (which may be renewed as often as appropriate). All serving REC members and bank members are indemnified by their appointing authority for their actions as co-opted members of any REC within the domain. If co-opted to a meeting of a REC outside the domain, a further letter of appointment and indemnity should be issued by the relevant appointing authority, prior to the meeting where possible.

2.42 A person should not be co-opted to attend more than six meetings, or more than six sub-committee meetings, of the same REC within any 12 month period. However, additional service may be undertaken as a co-opted member of another REC during this period.

Written comments from members

2.43 A member or deputy member who is unavailable to attend a meeting may submit comments in writing on any agenda item. These should normally be received by the Co-ordinator at least three working days prior to the meeting so that copies may be made available in advance to members. Where later comments are received, they may be tabled at the meeting at the discretion of the Chair. 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 ethical review.

2.44 A member or deputy member who submits written comments but does not attend the meeting either in person or by teleconference or videoconference does not count towards the quorum.
Referees

General policy

2.45 A REC may seek the advice of a referee on any aspects of an application that are relevant to the formation of an ethical opinion, and which lie 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.

2.45A Referee’s advice may be sought from a member of another REC as an individual (e.g. from a member with specialist expertise such as statistics) or from the REC collectively (e.g. from a flagged REC). Requests for such advice should be addressed via the Co-ordinator of the REC concerned. The response to the main REC should indicate clearly whether the advice is from an individual member or the REC collectively; if the latter, it should be agreed by sub-committee."

2.46 Referees are not voting members of the main 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.

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

(i) The Co-ordinator or Chair may write to the referee seeking written advice prior to the meeting. Letter SL4 should normally be used, 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.

(ii) The referee may be invited to attend the meeting in person for discussion of the application concerned. The attendance of the referee and the substance of his/her 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 decision taken by the REC.

(iii) The Committee may decide at the meeting to give a provisional opinion and seek written advice following the meeting. The Co-ordinator or Chair should normally write to the referee within 5 days of the meeting using SL9. The written advice received should then be considered promptly in accordance with procedures agreed at the meeting (see paragraphs 3.47-3.51 for further guidance).

2.48 The clock for ethical review does not stop while the advice of a referee is sought, only once a written request for further information is made.

2.49 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.
2.50 The opinion reached by the main 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 except with his/her express permission.

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CTIMPs involving minors or adults with incapacity

2.51 The REC is required under the Clinical Trials Regulations to obtain advice before giving its opinion on an application relating to a CTIMP in which any subject of the trial is:

(a) a minor, i.e. a person under the age of 16 years
(b) an adult incapable by reason of physical or mental incapacity to give informed consent to participation.

2.52 Where (a) applies and the REC has a member with professional expertise in paediatric care, his/her advice should be obtained on the clinical, ethical and psychosocial problems that may arise in relation to the trial.

2.532 Where (b) applies and the REC has a member with professional expertise in the treatment of the disease to which the trial relates and the treatment of the patient population suffering that disease, his/her advice should be obtained on the clinical, ethical and psychosocial problems that may arise in relation to the trial.

2.54 The following procedures apply to applications where either (a) or (b) applies.

2.55 If the relevant member is able to attend the meeting, his/her advice should be considered at the meeting and this should be recorded in the minutes.

2.55 If the relevant member is unable to attend the meeting, he/she should be invited to submit written advice prior to the meeting using SL4 or a suitable alternative. 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.

2.57 If the REC does not have a suitably qualified member, or the relevant member is unavailable to attend the meeting or to give written advice prior to the meeting, the REC has the following options:

- The Co-ordinator may explore with the REC operational manager whether a suitably qualified member or previous member of another REC, or previous member of the reviewing REC, may be co-opted.
- The Co-ordinator may explore with CAS or the REC operational manager whether the application can be transferred to another recognised REC with a suitably qualified member.
- If neither of these courses of action are possible, the REC should proceed with the review but should not give a final opinion until it has consulted a referee following the meeting, in accordance with paragraph 2.47(ii).
2.58 For the purposes of this section, a person with professional expertise may be any health care professional or a retired doctor or dentist with relevant expertise.

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Declarations of interest

2.59 Members and deputy members should declare to the Committee any material interests they may have in relation to an application for ethical review or any other matter for consideration at that meeting. Such a declaration may be made orally at the meeting, prior to the matter being considered, or in writing to the Chair prior to the meeting. 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 ethical review

2.60 Subject to paragraph 2.64, where the member concerned is the Chief Investigator or another key investigator/collaborator 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.

2.61 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. 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.

2.62 The Committee has the following options:

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

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

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

2.63 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 room as in paragraph 2.61(i) above.

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Site-specific assessments

2.64 Where a member or deputy member of a local REC is named on the SSI Form as the Principal Investigator or another member of the local research team, the procedures in paragraph 4.44 apply.

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Confidentiality of proceedings

2.65 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.

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

Observers

2.67 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 in form SF2, which is in line with the duty of confidentiality accepted by REC members.

2.68 External observers should have no vested interest in, or scientific or management responsibility for, any applications being considered at the meeting. In particular, 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 a 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 2.24, rather than as an observer.

2.69 Meetings, or parts of meetings, may also be attended from time to time by representatives of appointing authorities, REC operational managers, auditors, and other senior staff from NRES Head Office in accordance with governance arrangements for RECs (“official observers”). The Chair should be notified prior to the meeting.

2.70 Observers should take no part in the REC’s deliberations or decisions on particular applications.

2.71 If any observer is present, the Chair should verbally inform any investigator who attends the meeting. The investigator 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 room for that item. The attendance of observers should be recorded in the minutes.

Conduct of business and decision-making

2.72 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 officers are unavailable, the appointing authority for the REC should be invited to appoint another member of the Committee or a co-opted member as a temporary vice-Chair. If it is not possible to arrange formal appointment prior to the meeting, or if a temporary vice-chair is appointed at the meeting itself, the appointing authority should be asked to ratify the appointment retrospectively.

2.73 The Chair should have regard to NRES operational guidance on the conduct of meetings.

2.74 Vice-chairs may occasionally chair meetings when the Chair is present for training purposes, with the agreement of the REC operational manager. When doing so, they carry the normal responsibilities of the Chair.

2.75 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 individual votes, including abstentions. 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.

2.76 Where any member wishes to record his/her formal dissent from the decision of the Committee, this should be recorded in the minutes.

Responsibilities of the Co-ordinator

2.77 The secretary to the meeting will normally be the Committee Co-ordinator or an Assistant Co-ordinator.

2.78 The responsibilities of the Co-ordinator or Assistant Co-ordinator in relation to REC meetings are as follows:

(i) Publishing the schedule of REC meetings.
(ii) Preparing the agenda.
(iii) Allocating lead reviewers.
(iv) Distributing the agenda and papers.
(v) Inviting Chief Investigators and, where appropriate, supervisors to attend and making the necessary arrangements.
(vi) Preparing the venue.
(vii) Recording apologies for absence prior to the meeting.
(viii) Raising with the REC operational manager any concern that a meeting may not be quorate.
(ix) Recording attendance by members, deputy members, referees and observers for the discussion of each application for ethical review.
(x) Advising the meeting as necessary on compliance with standard operating procedures and, where relevant, the need for the REC to consider legal requirements applying to the ethical review (e.g. the criteria for approval under the Mental Capacity Act).

(xi) Making a written record of the meeting.

(xii) Recording individual votes where a vote is taken on a decision.

(xiii) Preparing the minutes of the meeting for review and approval at the following meeting.

(xiv) Notifying applicants of decisions taken at the meeting and taking other follow-up action as necessary.

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**Minutes**

2.79 The minutes of the REC meeting should be prepared by the secretary to the meeting in accordance with the guidance issued by the NRES Head of Operations. The substantive content of letters should be approved by the Chair before letters are issued to applicants giving the Committee’s decision (see paragraph 3.16). Local procedures should be agreed.

2.80 In relation to applications for ethical review or notices of substantial amendment, the minutes should contain a record of the following, whether in the main text of the minutes or in attachments:

(i) The members, deputy members, co-opted members, referees and observers present for the review.

(ii) Any interests declared, and the decision of the Committee on the participation of the member or deputy member concerned (see paragraphs 2.590-2.62).

(iii) The submission of written comments by members or deputy members (see paragraph 2.43)

(iv) The substance of any advice given by a referee (see paragraph 2.47(i)).

(v) The decision of the REC on the application (see paragraph 3.8).

(vi) A summary of the main ethical issues considered (see paragraph 3.19).

(vii) In the case of a favourable opinion, any conditions to be met prior to the start of the study (see paragraphs 3.23-3.28) or additional non-binding advice to be given to the applicant (see paragraph 3.29).

(viii) In the case of an unfavourable opinion, the reasons for the decision.

(ix) 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 (see paragraphs 3.10-3.11 and 3.35-3.39).

(x) Where no opinion is given, the issues on which further advice is required from a referee (see paragraph 3.38).
(xi) Where an unfavourable opinion is given on a notice of amendment, the reasons for the decision, and any delegation of responsibility for giving the opinion of the REC on a modified amendment (see paragraphs 5.39 and 5.43).

(xii) The outcome of any vote taken. (Individual votes should be recorded separately from the minutes.)

(xiii) Any formal dissent from the decision of the REC by a named member, with reasons.

(xiv) Whether an application was reviewed on a voluntary basis rather than as a requirement of policy or legislation (see paragraphs 1.93-1.94).

2.81 Except where 2.80(xiii) applies, the minutes should be presented as the outcome of collective discussion, and should not attribute particular statements to individual members or deputy members attending the meeting or providing written comments.

2.82 The minutes should be submitted to the following meeting of the REC for ratification as a true record. Any necessary revisions should be incorporated in the final version of the minutes. If the revisions are minor, they may be made in manuscript on the face of the minutes, and should be initialled and dated by the Co-ordinator. If not, a revised version of the minutes should be prepared. The final version should be signed and dated by the Chair and by the Co-ordinator or assistant Co-ordinator. Where revisions are made to the minutes, the Chair should consider the need to write to applicants correcting any inaccuracies or clarifying points made in the letter sent after the meeting. However, no substantially new request for information may be made at this point.

2.83 Subject to the provisions of the Freedom of Information Acts, the minutes should be treated as confidential to the REC and not routinely disclosed to applicants, sponsors or care organisations. For the purposes of REC governance, copies of minutes should be made available on request to the appointing authority for the REC, REC operational managers or auditors undertaking accreditation on behalf of NRES Head Office or the appointing authority. For guidance on retention of minutes, see paragraph 14.8.

2.84 The opinion of the REC on each application for ethical review should be published in the annual report. Further requirements for annual reports are set out in GAfREC.

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Section 3: Giving an ethical opinion

Summary

Guidance and training in ethical consideration is provided separately from the SOPs. This section of the SOPs describes the procedures for reaching and issuing the REC’s opinion on a new application.

Under the EU Directive and the Clinical Trials Regulations a REC must give an opinion on a CTIMP within 60 calendar days of receipt of a valid application, or 90 days where the trial involves gene therapy, somatic cell therapy, genetically modified organism or tissue engineered product. The 60 day period applies to all other research reviewed at full meetings.

Operationally the aim is to give an opinion within 40 days or, in the case of proportionate review by a sub-committee, 14 days.

Where a REC requires further information before confirming its opinion, it may give a provisional opinion and make one written request for further information, clarification or changes to documentation such as the participant information sheet. The clock stops until the REC receives a complete response to the request.

A REC should reach one of the following decisions following ethical review:

- Favourable opinion with standard conditions
- Favourable opinion with standard and additional conditions
- Unfavourable opinion
- Provisional opinion with request for further information, clarification or revision
- Provisional opinion pending consultation with a referee – a written request for information may be made following receipt of the referee’s advice
- No opinion – refer to full meeting for further review of significant ethical issues (proportionate review only).

If the committee gives a provisional opinion, it should specify what information is required and agree who is delegated to consider the further information and confirm the final opinion. This could be the Chair or vice-chair (supported by the REC office and in consultation with other members if necessary), a sub-committee, or exceptionally a meeting of the Committee.

Where required, a suitable referee should be identified as soon as possible. This could be a known specialist in the relevant field, or another REC in the domain. The referee should have no personal interest in the study, and the advice should remain confidential. The 60 day clock does not stop while advice is obtained.

The Co-ordinator notifies the Chief Investigator of the decision reached within 10 working days of the meeting, or 5 days following proportionate review. A standard letter for each type of opinion is obtained from RED. A final favourable opinion letter should include standard conditions of approval which the sponsor must ensure are met before the study starts.

The
REC may add other approval conditions if appropriate. Reasons for unfavourable opinions should be fully explained.

Where a Proportionate Review Sub-Committee gives no opinion, the application is re-booked for further review at a full meeting. The booking should be agreed with the applicant. A final opinion should be given within 60 days of receiving the original application.

A REC may vary its opinion where it emerges that it was based on factual error or misunderstanding. Requests to consider a variation of opinion may be made by the Chief Investigator or sponsor, or by responsible operational managers, and should be reviewed within 35 days.

Procedures for consulting regulatory bodies on relevant issues raised during ethical review, such as safety issues in CTIMPs, are set out separately in Section 13.

Detailed guidance on review of insurance, indemnity and compensation is in Annex G.
**Statutory and policy requirements**

3.1 Under the Clinical Trials Regulations, a REC is required to give an ethical opinion on an application relating to a CTIMP (except where paragraph 3.2 applies) within 60 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 give a provisional opinion and make one request in writing for further information from the applicant. The period of 60 days will be suspended pending receipt of this information.

3.2 In the case of a clinical trial involving (a) a medicinal product for gene therapy (b) a medicinal product for somatic cell therapy, (c) a medicinal product containing a genetically modified organism or (d) a medicinal product containing a tissue engineered product, the normal statutory time limit for review is extended to 90 days. This may be extended by a further 90 days (i.e. to 180 days in total) where the main REC needs to consult a specialist group or committee about the application. 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 ethical 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 all applications subject to a 60 day time limit, both CTIMPs and non-CTIMPs, the aim is for a final opinion to be given within 40 calendar days, allowing for the clock to stop once where a provisional opinion is given.

3.6 For applications accepted for proportionate review, the aim is for a final opinion to be given within 14 calendar days, allowing for the clock to stop once where a provisional opinion is given.

3.7 Guidance on the matters to be considered in the ethical review of research and training for REC members are provided separately by NRES with the support of the National Research Ethics Advisers’ Panel. 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.

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**Decisions available to the REC**

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

(i) Final opinion
The Committee may reach a final opinion on the application. This opinion may be either:

(a) favourable with standard conditions (see paragraph 3.21-3.23)
(b) favourable with additional conditions (see paragraph 3.24)
(c) unfavourable (see paragraphs 3.11, 3.30).

(ii) Provisional opinion with request for further information

The Committee may decide that a final opinion cannot be issued until further information or clarification has been received from the applicant (see paragraphs 3.8-3.10). It should indicate a provisional opinion in the initial review.

(iii) Provisional opinion 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 3.47-3.51). It should indicate a provisional opinion but not make a formal request for information at this stage.

or, in the case of applications reviewed by a proportionate review sub-committee only:

(iv) 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.

3.9 The Chair should ensure that one of the above decisions is made on every application considered at a Committee or sub-committee meeting.

3.10 Where the REC decides that further information or clarification is required, the Chair should ensure that:

- The further information or clarification required is specifically identified in the initial review.
- Delegation of responsibility for considering the further information and issuing the REC's opinion is clearly agreed (see paragraphs 3.29-3.32).

3.11 Requests for further information or clarification may include recommendations for revision of any of the supporting documentation, for example the participant information sheet and consent form. Clear guidance should be given to the applicant.

3.12 A proportionate review sub-committee may give a provisional opinion in the same way as the full Committee, including requests for information or clarification which will address straightforward ethical issues. Requests to submit changes to documentation may be appropriate where extensive rewriting of documentation is required and it will need to be re-checked by the Chair or lead reviewer before a favourable opinion can be confirmed. (Where the changes required are limited and can be easily specified, the sub-committee should consider giving a favourable opinion with conditions relating to the final version of documentation rather than a provisional opinion.) If there are significant ethical issues requiring wider discussion,
the sub-committee should give no opinion and refer the application for further review at a full meeting.

3.13 A proportionate review sub-committee may give an unfavourable opinion only on the grounds that the application is of such poor quality that it is probable that an unfavourable opinion would be given if it were to be reviewed at a full meeting and any further review without substantial changes to the application would be an unjustified use of the resources of the Research Ethics Service. The sub-committee may not give an unfavourable opinion for any other reason. If there are significant ethical issues requiring further discussion, the application should be referred for further review at a full meeting.

3.14 The Co-ordinator 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.

3.15 The decision taken on each application should be entered on RED.

Notification of the decision to the Chief Investigator

3.16 The Co-ordinator should ensure that notification of the decision is sent to the Chief Investigator in writing within 10 working days of a full meeting, or within 5 working days of proportionate review by sub-committee. In the case of projects undertaken primarily for educational purposes, the decision letter 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, who has ultimate responsibility for, and should approve, the content. It is acceptable for the letter to be signed by a vice-chair or member of the REC office acting under delegated authority from the Chair. Local procedures should be agreed (see also paragraph 2.79). One of the following letters should be used:

Applications reviewed at a full meeting:

- SL5 Favourable opinion
- SL6 Unfavourable opinion
- SL7 Provisional opinion with request for further information
- SL8 Provisional opinion pending consultation with a referee.

Applications reviewed by sub-committee under proportionate review:

- SL5 (PR) Favourable opinion
- SL6 (PR) Unfavourable opinion
- SL7 (PR) Provisional opinion with request for further information
- SL8 (PR) No opinion – application referred to full meeting

3.17 The following information should in all cases be included in the letter or in enclosures:
• A summary of the ethical issues considered by the REC.
• A list of all documents reviewed at the meeting, giving 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. The list should indicate lay members and give the profession in the case of expert members.
• 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.)
• The names of any observers present at the meeting.
• A named contact point (normally the Co-ordinator) for receipt of queries from the applicant. (The REC should agree which members will be available to support the Co-ordinator in handling queries.)

3.18 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).

3.19 The summary of ethical issues should set out the main issues considered by the REC in deciding on its opinion. It is not necessary to include all the questions raised at the meeting, such as requests by lay members for explanation of technical points. However, it is important to record for future reference any ethical issues that the REC collectively discussed and resolved with the Chief Investigator at the meeting, and any clarifications given orally of the information contained in the application. It should not then be essential for the Chief Investigator to provide written confirmation on these points, unless the REC considers that further information, clarification or revision of the documentation is required after the meeting.

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

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Final opinion letters

3.21 All letters issuing the REC’s final opinion should be in the name of the Chair of the Committee (or sub-committee in the case of proportionate review), who has ultimate responsibility for, and should approve, the content. It is acceptable for the letter to be signed by a vice-chair or member of the REC office acting under delegated authority from the Chair. The letter should be posted to the applicant within the relevant time limit for review of the application (see paragraphs 3.1-3.4)

3.22 The opinion of the REC should be entered on RED. The date of the opinion is the date on which the final opinion letter is sent.

Favourable opinion
3.23 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 site). 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.

3.24 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 site. In the case of studies requiring SSA (see Section 4), the suitability of NHS sites is assessed by the NHS R&D office as part of standard R&D review. The favourable opinion therefore applies to all NHS sites on condition that NHS management permission is obtained prior to the start of the study at that site.

3.25 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.

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

- Specific additions or amendments to the participant information sheet or other study documentation. *(Note: The additional information and/or wording required should be clearly specified by the REC such that responsibility for implementing the changes can be given to the sponsor and no further ethical review will be needed. It would not be appropriate, as a condition of the final opinion, to require significant and unspecified revisions of documentation that might require further consideration by the REC.)*

- Requirement for the Chief Investigator to undertake training in informed consent or GCP;

- 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;

- Obtaining or renewing a final certificate of insurance or indemnity to provide the cover specified in the REC application. *(Note: Details of the proposed cover must be provided in the application form as part of a valid application, but issue or renewal of the final certificate may follow after issue of a favourable opinion.)*

3.27 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 ethical 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.

3.28 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 sites) and provide copies of final documentation for reference purposes where appropriate. The Co-ordinator should acknowledge receipt within 5 working days using SL44. Neither the REC nor the Co-ordinator is required to undertake any further review of the actions taken, or to confirm approval of final versions of amended documentation.

3.29 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 ethical 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 amendments (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.

3.30 In the case of studies requiring site-specific assessment (SSA), the REC reviewing the application (“the main REC”) should confirm approval of each non-NHS site as part of the ethical opinion.

3.31 Where a study requires SSA and includes non-NHS sites, there may be occasions where the main REC is in a position to issue a favourable opinion but no SSA has yet been carried out. In such cases, the Co-ordinator should issue the favourable opinion without delay (see paragraph 4.59).

Unfavourable opinion

3.32 Where the final opinion is unfavourable, the applicant should be given a full explanation of the REC’s reasons. The applicant should also be informed of the options available for further review (see paragraph 3.59 and Section 7).

3.33 In a CTIMP or a clinical investigation of a medical device, the REC should consult the MHRA before giving an unfavourable opinion where the reasons include issues relating to the safety of the trial or the sponsor’s planned arrangements for safety monitoring, and should take its advice into account. It is recommended that, where the REC is minded to give an unfavourable opinion on such grounds, it should issue a provisional opinion setting out the issues of concern, invite the sponsor to provide further information addressing these points and consult the MHRA in parallel. Procedures for consulting MHRA are set out in Chapter 13.

3.34 Following an unfavourable opinion on a CTIMP, the Co-ordinator should complete the EudraCT checklist of reasons for the opinion in RED within two working days of issuing the opinion letter. These reasons should be checked and signed off by the operational manager within a further three working days and then notified to MHRA via RED for upload to EudraCT.
Provisional opinion and request for further information

Delegation of responsibility

3.35 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. These responsibilities should normally be delegated to one of the following:

(i) Chair or vice-chair or lead reviewer alone, with support from REC office staff;
(ii) Chair or vice-chair, in oral or written consultation with one or more named members or deputy members that were present at the meeting or who submitted written comments on the application, or with a Scientific Officer;
(iii) Sub-committee involving named members (see paragraph 6.8).

3.36 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. Where the information is straightforward, it is acceptable for the matter to be delegated to the Chair alone. (If the information is purely administrative or very straightforward, for example minor corrections to the participant information sheet, it is acceptable for the Chair to delegate his/her responsibility to REC office staff.) Where the information is technical or any questions of judgement are likely to arise, the Chair should personally review the information. Consideration should be given to involving other members, 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.

3.37 Following proportionate review, the further information or changes to documentation requested with the provisional opinion will normally be reviewed by the lead reviewer.

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

3.39 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 four 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

3.40 The clock should be suspended from the date on which the request for further information was sent to the applicant. It should be re-started on the date when a complete response is received (“the re-start date”).
3.41 Where the response arrives piecemeal, the re-start date is the date on which the final part of the response is received.

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

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Requirement for a complete response

3.43 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 Co-ordinator should write to the applicant using SL11 or SL11 (PR) as applicable, 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 Co-ordinator contacts the applicant (or arranges for the Chair or lead reviewer to do so) 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.

3.44 The applicant should normally be allowed a period of four months to respond to the request for further information. The REC may extend this period at the request of the applicant where there are reasonable grounds for requiring more time to respond. If the applicant has not responded with one month remaining of the period allowed, a reminder letter should be sent using SL12. If no response is received within one further month, the Co-ordinator should send SL13 advising that the REC considers the application to have been withdrawn. The applicant would then be required to submit a new application in order to obtain an ethical opinion.

3.45 The response to the Committee’s request for further information should be provided personally 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. Responses by e-mail are generally acceptable but the REC has the discretion to require a signed letter.

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Final opinion following consideration of the information

3.46 On receipt of a complete response from the applicant, the REC should issue its final opinion on the application, which may be favourable or unfavourable. The procedures set out in paragraph 3.17-3.22 should be followed. One of the following letters should be used:

SL14 Favourable opinion following consideration of further information
SL14 (PR) Favourable opinion by PRSC following consideration of further information
Further advice from a referee

3.47 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 issue a provisional opinion but defer the request for further information. SL8 should be used to explain that REC will be consulting a referee and will write 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 to 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.

3.48 In some cases, the REC may decide at the meeting who it wishes to consult, and if so this should be recorded in the minutes. If not, either the Chair or the Co-ordinator should be appointed to identify a suitable referee urgently following the meeting. The REC may wish to seek advice from the REC operational manager, who may be aware of members of other RECs with the relevant expertise, or from senior operational management at NRES Head Office. The referee may be another REC or specialist body.

3.49 The Chair or Co-ordinator should initially contact the prospective referee by phone or e-mail to establish whether he/she is 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 paragraphs 2.49-2.50).

3.50 Once a suitable referee has been identified, the Co-ordinator should write to the referee, using SL9. This 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 5 working days of the meeting. The referee should be asked to respond in writing within a further 10 days.

3.51 Once the referee’s advice has been received it should be considered promptly by the Chair and/or lead reviewer, or by a sub-committee of specified members (as determined at the full meeting). If it is decided to make a request for further information or clarification at this point, SL10 should be issued, taking into account the advice of the referee. The clock stops at this point. The procedures in paragraphs 3.35-3.46 apply to further review and issue of the final opinion following the response from the applicant. If a final opinion can be reached in the light of the referee’s advice, SL14 or SL15 should be used with adaptations.

No opinion and referral to full committee

3.52 Where a proportionate review sub-committee gives no opinion under paragraph 3.8(iii), the application should be referred for review at a meeting of a full REC, normally another committee within the same REC centre.
3.53 The Co-ordinator should first contact the Local Allocation Service (LAS) to identify the next suitable agenda slot at a full REC meeting. The applicant should then be contacted by phone or email to explain that the application is being referred to a full meeting and seek the applicant's agreement to the allocation and proposed meeting date. If the applicant agrees, the clock is not stopped during the transfer process. Should the applicant refuse the first allocation, an alternative slot should be offered and agreed with the applicant. In this case, the validation date should be reset to the closing date for submissions to the meeting concerned. Once the allocation is agreed, the Co-ordinator should send SL8 (PR) confirming the No Opinion decision and the arrangements for further review. The reasons for referral to a full REC should be explained. All paperwork connected to the application should then be sent to the new REC for their information.

3.54 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 gives a provisional opinion with a request for further information in writing.

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**Regulatory approval**

3.55 It is the responsibility of the sponsor to ensure where necessary that a research study has appropriate regulatory approval as well as a favourable ethical 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 13.

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**Insurance, indemnity and compensation**

3.56 Before confirming a favourable opinion on any research (including both CTIMPs and non-CTIMPs), the main 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 G.

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**Notifying other bodies of the progress of applications**

3.57 It is generally the responsibility of the Chief Investigator to inform other interested bodies of the progress of the ethical review. The REC system 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 policy from NRES Head Office s that the REC system should take reasonable steps to facilitate good communication between those concerned.
3.58 Standard procedures for the copying of correspondence are as follows:

(i) The main 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.

(ii) Where the study involves NHS sites, the main REC should send copies of correspondence to the lead R&D office for the study. 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 main REC confirming the favourable opinion for the study and for the site.

(iii) RECs undertaking site-specific assessment at non-NHS sites should send a copy of the letter validating the SSA (SL17) to the sponsor’s representative.

3.59 Procedures for communicating with other regulatory bodies during initial review and following the start of a study are set out in Section 13.

Variation of the opinion

3.60 Where a REC has given a final opinion, either favourable or unfavourable, 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:

- Understanding of the application or the further information provided by the applicant or advice from a referee
- Interpretation of relevant legal or regulatory requirements
- Application of other published guidance to the conduct or management of the study.

3.61 An unfavourable opinion may be varied to a favourable opinion where the reasons for the opinion no longer apply.

3.62 A favourable opinion may be varied by issuing a new favourable 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 provisional opinion or the conditions attached to the final opinion.

3.63 A variation of the opinion may be requested by the Chief Investigator or sponsor by writing to the Chair of the REC, copied to the REC operational manager. A variation may also be requested by the REC operational manager after consultation with the CI and sponsor.
3.64 Requests to vary the opinion should be considered by the REC either in sub-committee or at a full meeting and a decision communicated to the CI within 35 days of receipt of the request. Where the opinion is varied, the Co-ordinator 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.

**Corrective action following legally invalid opinion on a CTIMP**

3.65 Annex D 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**

3.66 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 ethical opinion on the trial that it is organised and operates according to GCP. All the REC standard letters issuing ethical 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 ethical review indicating lay members and stating the profession of expert members. The statement of compliance also explains that the constitution of a REC is as defined in GAfREC and its operating procedures are defined by the national SOPs issued by NRES Head Office. No additional documentation needs to be provided to sponsors. In particular, there is no requirement to provide details of local REC members or other individuals involved in site-specific assessments.

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**Publication of opinions**

3.67 Requirements for the publication of decisions in the REC’s annual report are set out in GAfREC.

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**Approval to proceed with research**

3.68 A favourable opinion from a REC does not imply management (i.e. research governance) approval from relevant care organisation(s) to proceed with the research. Applicants should be informed of the requirement to apply separately to each care organisation for research governance approval. The R&D offices of NHS
care organisations may indicate approval in principle prior to the ethical review, but will not give final approval to proceed until a favourable ethical opinion and, where applicable, regulatory approval have been confirmed.
Section 4: Site-specific assessment

Summary

Under the EU Directive and the Clinical Trials Regulations there can be one ethical review only for any CTIMP in the UK. The policy of the UK Health Departments is that this should apply to the ethical review of all research in the NHS.

Clinical research and studies involving adults unable to consent for themselves normally require site-specific assessment (SSA) for each site as part of the ethical review. The process of SSA may take place in parallel with the main review.

Guidance is given to applicants and RECs on the definition of a research site. Normally this will be a single NHS organisation but could also be a discrete operating unit within a NHS organisation, or a network of researchers, or a research unit outside the NHS. Each site should have a single Principal Investigator, who is responsible for the management and conduct of the research at the site.

SSA at NHS sites is the responsibility of the NHS R&D office and is integrated into the normal research governance review required for all research conducted in or through the NHS. The favourable opinion from the main REC is given on condition that permission is given by the R&D office. No review of site-specific issues is undertaken by the main REC or by local RECs.

SSA at non-NHS sites is the responsibility of the REC system. The REC undertaking the SSA is known as the “SSA REC” and may be either the main REC or an appropriate local REC. Designated SSA RECs may be appointed for specialist research units outside the NHS.

Exceptionally, the main REC may give exemption from SSA where specified criteria are met. Local Principal Investigators may submit applications for SSA as soon as the main application for ethical review has been validated. The application comprises the SSI form, the PI’s CV, local versions of recruitment documentation and evidence of insurance or indemnity cover where required.

Guidance is given on issues relevant to the SSA at non-NHS sites. The SSA REC is not responsible for wider ethical issues raised by the research. It may draw wider concerns to the attention of the main REC but should not raise formal objections except on site-specific grounds. The main REC may over-rule objections if satisfied that they are not valid.

SSA is a documentary check that may be undertaken in correspondence involving at least 2 members including the Chair, or at a sub-committee or Committee meeting. The PI may be invited to attend a meeting. Clarification of issues relevant to the SSA may be sought. Exceptionally, a site visit may be arranged where the SSA REC is not familiar with the site.

The SSA REC has 14 days (for a Phase 1 trial) or 25 days (other studies) from receipt of a valid application to notify the main REC of the decision. The main REC then informs the Chief Investigator whether it has given a favourable opinion for the site. The CI is responsible for notifying each PI when the site has been approved.
Neither the main REC nor the SSA REC is responsible for proactive monitoring of the conduct of the research at the site. However, if concerns arise the main REC may request a new SSA and review the favourable opinion for the site. The SSA REC may itself instigate a new SSA and should report any new concerns to the main REC.
General policy on multi-site studies

4.1 In the case of a clinical trial of an investigational medicinal product, the Clinical Trials Regulations provide that a single ethical opinion should be given on any trial, regardless of the number of sites at which the research is to be conducted.

4.2 The policy of the Department of Health and the devolved administrations is that the requirement for a single ethical opinion should apply generally to all multi-site research within the UK. The only exception to this is where for non-CTIMPs involving adults unable to consent for themselves and taking place at sites in both England or Wales and Scotland. In this case, two separate opinions must be given under the legislation applying in each jurisdiction (see paragraph 12.57).59).

4.3 The Chief Investigator for any study should therefore submit a single application for ethical review, which should be allocated for review as specified in Section 1. The REC that reviews the application is referred to in this section as the “main REC”. The main REC is responsible for all aspects of the ethical review.

Requirement for site-specific assessment

4.4 For certain types of study, the ethical review includes an assessment of the suitability of each site or sites at which the research is to be conducted in the UK. The “site-specific assessment” (SSA) is not a separate ethical review, but forms part of the single ethical review of the research. Where there is no objection from the assessor on site-specific grounds, a site is deemed to be approved as part of the favourable ethical opinion given by the main REC.

4.5 Except where paragraphs 4.27-4.29 apply, SSA is required for all sites in the following types of study:

(i) Clinical trials of investigational medicinal products (CTIMPs)
(ii) Clinical investigations of non-CE marked medical devices or CE marked devices which have been modified or are being used for a new intended purpose
(iii) Combined CTIMPs and clinical investigations of medical devices
(iv) Other clinical trials to study a novel intervention or randomised clinical trials comparing interventions in clinical practice
(v) Intrusive research involving adults unable to consent for themselves in England or Wales and requiring approval under the Mental Capacity Act 2005, and similar research in Northern Ireland
(vi) Research involving adults unable to consent for themselves and requiring approval under the Adults with Incapacity (Scotland) Act 2000.

4.6 For research falling outside the categories listed in paragraph 4.5, SSA is not required for the purposes of ethical review. All research sites listed in the application to the REC, and any other sites added during the course of the study, are deemed to be ethically approved as part of a favourable opinion from the REC. Management permission is still required from the organisation responsible for hosting the research before it commences at any site.

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The Principal Investigator

4.7 In the case of any single or multi-site clinical research, the investigator responsible for the conduct of the research at an individual research site will be known as the Principal Investigator for that site. There should only be one Principal Investigator at each site.

4.8 A “single site study” is a study that the Chief Investigator plans to conduct at one site only in the United Kingdom. The Chief Investigator will in most cases also be the Principal Investigator for the site. In the case of a single-site CTIMP, the CI and PI must be the same person.

4.9 A “multi-site study” is a study that the Chief Investigator proposes should be conducted at more than one site in the UK. The Chief Investigator may also be the Principal Investigator for one of the sites (known as the “lead site”). At other sites, a Principal Investigator should be appointed. It is the responsibility of the Chief Investigator to ensure that a suitably qualified professional is appointed as the Principal Investigator for each site. In a CTIMP, the Principal Investigator and all other named investigators must be “authorised health professionals” (see definition in the Glossary).

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

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Definition of a research site

4.11 Under the Clinical Trials Regulations, a “trial site” means a hospital, health centre, surgery or other establishment or facility in the UK at or from which a CTIMP, or any part of a CTIMP, is conducted. For administrative purposes, the guidance set out below applies to the definition of a research site in any study submitted to a REC in the UK.
4.12 In general, the research site should be identified as the single organisation responsible for hosting the research at a particular locality.

4.13 In the case of research conducted within the NHS, the site will in most cases be one of the following:
   - A NHS Trust (in England or Wales)
   - A NHS Health Board (in Scotland)
   - A Health and Social Care Trust (in Northern Ireland)
   - A GP practice or NHS dental practice.

4.14 Where the research will be conducted at more than one location within the same organisation (for example, where the departments involved are dispersed at different hospitals within an acute Trust or Health Board), this should normally be considered as a single site.

4.15 Exceptionally, where the research is to be conducted in two or more entirely discrete operating units within the same NHS organisation, these units may be separately identified as research sites. Each site should have its own Principal Investigator who is accountable for the whole research team. There should be no dual accountability or overlap between research teams. These criteria might apply for example to the operating divisions or community health partnerships established by NHS Health Boards in Scotland. They do not apply to separate clinical departments within the same acute Trust.

4.16 For research conducted by GPs and NHS dentists, the Primary Care Trust (England), Health Board (Scotland), Local Health Board (Wales) or Central Services Agency (Northern Ireland) is the "organisation providing care" as defined in the NHS Research Governance Framework. However, the GP or dental practice should normally be identified as the research site as it provides contractual services to the care organisation as an independent practitioner. The following scenarios should be noted:
   - Where two or more GPs or dentists are conducting a study within the same practice, it should be regarded as a single site and one of the practitioners should be appointed as the Principal Investigator.
   - In some cases, two or more independent practices may be conducting the research within the same health care centre. These practices should normally be identified as separate research sites.
   - Where, however, two or more practices have contracted to conduct research collaboratively, whether through a network/consortium or under the direct management of the care organisation, they may be collectively identified as a single site. In such cases, one of the investigators should be appointed as the Principal Investigator for the site. Researchers other than GPs and dentists may also be involved in the network/consortium.

4.17 A Primary Care Trust, Health Board, Local Health Board or the Central Services Agency may itself be identified as the research site in the case of research being
conducted into primary, community or social care services that it manages directly. However, in England, Wales and Northern Ireland, where the investigator is employed by the primary care organisation but provides services to an acute Trust on its premises, the research site will normally be the acute Trust. In Scotland, both primary and acute care services are managed by Health Boards.

4.18 A Strategic Health Authority in England could be identified as the research site for some research, for example studies in public health, epidemiology or needs assessment.

4.19 Research sites outside the NHS could include the following:

- an academic institution
- a research centre funded by the voluntary sector
- a Government Department or other public body
- a Prison Service establishment, local authority secure unit or Home Office secure training centre
- a private company or corporation (for example, a pharmaceutical or biotechnology company or clinical research organisation)
- a private hospital or private clinical practice
- an employee-led social enterprise.

Where the research site is outside the NHS in terms of accountability but the Principal Investigator 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 site should be clearly distinguished from the NHS organisation concerned.

4.20 In some cases, a study hosted by a NHS care organisation may involve routine protocol procedures being undertaken by non-NHS organisations under contractual arrangements with the NHS organisation. For example, MRI scans or laboratory analysis may be undertaken on premises owned by universities, research charities or private companies. These arrangements may be considered as a single NHS site where all of the following conditions are met:

- All the participants are NHS patients recruited through the NHS organisation
- The relevant NHS R&D office (which may be a joint research office acting on behalf of more than one organisation) assumes full responsibility under the Research Governance Framework for all procedures involving NHS patients at the site, including those undertaken by non-NHS organisations
- Indemnity for all procedures is in place under the Clinical Negligence Scheme for Trusts (“NHS indemnity”).

Where any of these conditions are not met, the non-NHS organisation should be considered a separate site.
4.21 Research sites are organisations responsible for participant-related research procedures specified in the protocol, including recruitment and informed consent. The following are not considered to be research sites:

- 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;
- Research units undertaking support functions, e.g. project management, site monitoring, data analysis, report writing.

Responsibility for undertaking SSA

SSA at NHS sites

4.22 Under the Research Governance Framework for Health and Social Care, management permission through the R&D office ("R&D approval") is required to conduct research at any site within the NHS or Health and Social Care in Northern Ireland (HSC). Application for R&D approval is made by submitting the main R&D application form in IRAS, together with the Site-Specific Information (SSI) Form for the site. Guidance on R&D application procedures is available at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk) and within IRAS.

4.23 For research requiring SSA as part of the ethical review, the SSA is undertaken by the R&D office as an integral part of its governance review prior to giving approval. The information required for SSA is incorporated within the SSI Form for NHS sites in IRAS. No separate application for SSA is required. SSI Forms do not need to be submitted to the main REC or local RECs.

4.24 A standard condition of a favourable opinion from the main REC is that management permission is obtained before the start of the study at each site (see paragraph 3.24). There is no requirement for the outcome of the SSA or the final decision on R&D approval to be notified to the main REC by the R&D office, or for the main REC to confirm ethical approval for each site. Once management permission has been given, the site is deemed to be ethically approved as part of the favourable opinion.

SSA at non-NHS sites

4.25 Responsibility for undertaking SSA at non-NHS sites in the UK lies with the REC system itself. The REC responsible ("the SSA REC") will normally be a REC in the geographical area where the site is located. The main REC may also be a SSA REC for a particular site or site(s). All RECs within the scope of these SOPs are authorised to undertake SSA in any type of study. In the case of a CTIMP, the REC does not need to be recognised by UKECA.

4.26 Where there is doubt about which REC should undertake SSA for a particular site, the sponsor or Principal Investigator should contact the REC operational manager for
advice. It is the responsibility of the operational manager to identify a suitable REC. Designated SSA RECs may be appointed for non-NHS sites regularly involved in research requiring SSA, e.g. research units in the commercial, higher education or voluntary sectors. For commercial Phase 1 trials in healthy volunteers, a list of designated SSA RECs for each trial unit in the UK has been agreed by NRES and AAPEC and is published on the NRES website. Application for SSA should always be made to a designated SSA REC where applicable.

Exemption from the requirement for SSA at non-NHS sites

Non-clinical research involving adults lacking capacity to consent

4.27 The main REC has the discretion to waive the requirement for SSA at non-NHS sites in the case of research involving adults lacking capacity to consent for themselves where the study involves no clinical interventions and either of the following apply:

(i) Studies with no local investigator. All recruitment procedures and all study procedures involving participants (e.g. questionnaires, observations) are undertaken directly by the Chief Investigator’s team. The role of local staff at the site is limited to facilitating the study, for example by helping to identify potential participants and relatives/consultees, who are then approached by the Chief Investigator’s team.

(ii) Low risk studies. In this case, SSA may be waived where the main REC is satisfied that the risk to participants lacking capacity is likely to be negligible and will not interfere with their freedom of action or privacy in a significant way or be unduly invasive or restrictive. These criteria could apply for example to studies limited to use of personal data, or the administration of a simple questionnaire involving minimal burden.

4.28 When giving exemption for SSA under paragraph 4.27, the main REC should be satisfied from review of the main application that the Chief Investigator’s team will make adequate arrangements for the conduct of the study locally, including procedures for identifying suitable sites, participants and relatives/consultees. Where local site staff will be responsible for undertaking recruitment or other study procedures, the main REC should be satisfied that they will have appropriate training. Approval conditions may be included in the ethical opinion where appropriate (see paragraphs 3.19-3.24).

4.29 The Chief Investigator or sponsor may submit a request for SSA exemption under paragraph 4.27 either with the main application or in further correspondence at any time. However, the Committee may decide to give exemption without receiving such a request. Decisions to give exemption may be made at a meeting of the Committee or sub-committee, or by the Chair acting alone. The Chief Investigator and sponsor should be notified using SL1A or by incorporating the relevant text into the validation or opinion letter.

Subsidiary sites in clinical research

4.30 In clinical research the main sites undertaking recruitment and administering the interventions will always require SSA. However, it may be necessary to arrange for
routine clinical procedures required by the protocol to be carried out by other organisations sites in support of the research. For example, routine imaging using standard clinical protocols may be undertaken by a private scanner centre under contractual arrangements with the NHS care organisation where the participants are recruited. Unless the NHS organisation accepts full governance responsibility for these procedures and assures NHS indemnity (see paragraph 4.20), the responsible non-NHS organisation should be considered a separate research site or ‘subsidiary site’. Management permission is required from the organisation responsible for the subsidiary site. However, the Chief Investigator or sponsor may request exemption of non-NHS subsidiary sites from the requirement for SSA by writing to the main REC giving the name and address of the subsidiary site, the name of the person who will act as local Principal Investigator (i.e. take responsibility for the conduct of study procedures) and brief details of the routine procedures to be conducted. The request may be reviewed by the Chair or by sub-committee or at a meeting of the Committee. The Chief Investigator and sponsor should be notified of the decision using SL1A or by incorporating the relevant text into the validation or opinion letter. (Note however that where the NHS organisation accepts full governance responsibility for procedures at the non-NHS organisation, this is considered a single site and SSA exemption is not required).

Application for site-specific assessment at non-NHS sites

4.31 Where the SSA is to be undertaken by the main REC, the application for SSA should normally be included with the main application for ethical review. However, application may be made at any time subsequently.

4.32 Applications for SSA may be made by local Principal Investigators at other non-NHS sites as soon as – but not before - the Chief Investigator for the study has been notified by the main REC that the application for ethical review is valid. It is not necessary to wait for the issue of a favourable ethical opinion. The ethical review and the SSA should normally proceed in parallel, so that the outcome of the SSA can be included in the ethical opinion given by the main REC within the time limit of 60 days.

4.33 The Principal Investigator should submit the application for SSA to the SSA REC electronically from IRAS\(^\text{12}\).

4.34 It is not necessary for the Principal Investigator to book a meeting agenda slot for a SSA application. Such applications may be submitted at any time. However, Principal Investigators may contact the REC office beforehand so that advice can be given about local arrangements for SSAs.

\(^{12}\) See paragraph 11 of the Introduction to the SOPs in relation to implementation of arrangements for electronic submission.
4.35 Where the main REC is also the SSA REC for the lead site, it should carry out the SSA for this site alongside the ethical review.

4.36 The application should be accepted as valid if it meets all the following criteria:
   i. The Site Specific Information Form and all supporting documentation have been submitted electronically from IRAS.
   ii. All relevant sections and questions in the SSI form have been completed, and the text is in English and legible.
   iii. The SSI form has been electronically authorised by the Principal Investigator.
   iv. Short curriculum vitae (maximum two pages) have been submitted for the Principal Investigator. (It is not necessary to submit CVs for other staff.)
   v. The site is located in the United Kingdom.
   vi. The name of the site has been correctly stated on the SSI form, taking into account the guidance in paragraphs 4.11-4.21.
   vii. Local versions have been provided on headed paper of all documentation to be used to recruit participants at the site, including documentation for relatives/consultees in the case of adults lacking capacity.
   viii. Evidence of insurance or indemnity cover for the Principal Investigator has been provided (except for commercial Phase 1 trial sites).
   ix. Evidence of professional registration for the Principal Investigator has been provided.

4.37 If the application is valid, the SSA REC Co-ordinator should acknowledge receipt by writing to the Principal Investigator using SL17. A copy should be sent to the sponsor’s contact point.

4.38 If the application is not valid, the Principal Investigator should be notified of the reason(s) using SL18.

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Issues relevant to the site-specific assessment

4.39 In making a site-specific assessment, the main issue to be considered is the suitability of the site for the conduct of the research. This involves consideration of the following:

   (i) The suitability of the Principal Investigator, taking into account his/her professional qualifications, knowledge of the research field, expertise in the procedures involved, previous research experience, training in research methods (including informed consent), training in Good Clinical Practice (if applicable), and ability to take professional responsibility for the local research team.

   (ii) The adequacy of the local facilities available for the research.
(iii) In a CTIMP, arrangements for receipt and storage of trial medication, Qualified Person Certification (if applicable), reconstitution (if applicable), labelling, control of access, dispensing, record-keeping and destruction.

(iv) The arrangements for notifying other local health or social care staff, who may have an interest in the care of the participants, about the research.

(v) The availability of any extra support that might be required by research participants as a result of their participation.

(vi) For studies involving adults unable to consent for themselves, the local arrangements for identifying and approaching a legal representative (CTIMPs), the guardian, welfare attorney or nearest relative (non-CTIMPs in Scotland), a consultee under section 32 of the Mental Capacity Act (non-CTIMPs in England and Wales) or a close relative or friend (non-CTIMPs in Northern Ireland). This includes consideration of the appointment and training of professional legal representatives or nominated consultees. The SSA REC may request additional documentation where appropriate.

(vii) The practical arrangements to be made at the site for providing information to potential participants who might not adequately understand verbal explanations or written information given in English, where it is planned to include such groups in the study as a whole. (Where the Chief Investigator proposes in the main application that such groups are to be excluded, this is an ethical issue for the main REC rather than the SSA REC. However, if the main REC does not accept the reasons given and requires their inclusion, the SSI form should be revised and new applications for SSA should be made.)

(viii) Inclusion of relevant site-specific information in the local version of the information sheet for the study or in additional standard information for local research participants, including the following:

(ix) The address and telephone number of the site (normally to be included on the headed paper to be used locally)

(x) The organisation responsible for conducting the research at the site.

(xi) Contact details for the local investigator(s) and, if applicable, other staff such as research nurses

(xii) Emergency contacts if appropriate

(xiii) Contact information for complaints and, where appropriate, independent advisers.

(xiv) Evidence of insurance or indemnity to cover the potential liabilities of the Principal Investigator. (Note: This is not required for commercial Phase 1 trials in healthy volunteers as the sponsor makes an undertaking to compensate a volunteer who has suffered harm as a result of taking part in the trial whether or not the sponsor is liable. The sponsor company will make its own arrangements to ensure that the CRO and Principal Investigator have sufficient insurance or indemnity cover so that it can recover any losses from them where the harm resulted from their negligence. The sponsor’s insurance cover will be reviewed by the main REC.)
Evidence that the Principal Investigator has appropriate professional registration.

Additional documentation may be requested relating to the governance of the research site, for example internal SOPs, protocols, quality standards, job descriptions, training policies, evidence of audit and inspection. (Where the site is a specialist research unit, e.g. for Phase 1 trials in healthy volunteers, the SSA REC will not need to request documentation for each study.)

4.40 The Principal Investigator is formally accountable for the whole research team, and it is not necessary for the SSA to give detailed scrutiny to the suitability of other local investigators or support staff, or to require submission of other CVs. Questions about the proposed conduct and management of the research at the local site may be raised directly with the Principal Investigator, including the allocation of research tasks to staff with relevant expertise and procedures for monitoring and supervision. Any assurances or clarifications given by the Principal Investigator should be noted in the record of the assessment (see paragraph 4.43).

4.41 Site-specific assessment does not involve any consideration of other issues relating to the ethical review of the application, which is the sole responsibility of the main REC. The assessor may not request correspondence relating to the main ethical review.

Procedures for SSA for non-NHS sites

4.42 The assessment should be made by at least two members, including the Chair or a vice-chair. It may be carried out in correspondence, including e-mail. Alternatively the assessment may be made at a meeting of the sub-committee or at a full meeting of the REC.

4.43 Where the assessment is made in correspondence, the Chair or vice-chair is responsible for reviewing the comments made by other members and for making a final decision on behalf of the REC. Any relevant questions or concerns should be addressed appropriately with the Principal Investigator (see paragraph 4.45). Where there are significant objections, or a difference 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. The Co-ordinator should prepare minutes of assessments made in correspondence which should include the names of the members involved, all comments received and the outcome of the assessment.

4.44 Where a member or deputy member of the SSA REC is involved in the conduct of the research, whether as an investigator, key collaborator or local research team member, the SSA should normally remain the responsibility of the REC to which it is submitted. The member or deputy member concerned should take no part in the assessment other than providing additional information at the request of the assessors. He/she may attend any meeting to answer questions but should leave the meeting room while the assessment is discussed and a decision made.
4.45 Every effort should be made to address relevant questions with the Principal Investigator within the time allowed for the SSA. The Principal Investigator may be required to respond to questions in writing or by telephone, or invited to attend a Committee or sub-committee meeting. A file record should be kept of any telephone conversation. If the Principal Investigator does not respond or provide adequate assurances, objections may be raised. If further information is received subsequently that resolves the issues, this should be reported to the main REC (see paragraph 4.64).

4.46 The SSA REC should ensure that the assessment is made and the main REC notified of the outcome within 14 days of receipt of a valid application (in the case of commercial Phase 1 trials in healthy volunteers) or 25 days (all other studies). It is generally the responsibility of the REC operational manager to monitor compliance with these timelines, using management information on RED. If in a particular case the main REC has not been notified of the outcome within the timeline, the Coordinator may follow this up directly with the SSA REC Coordinator by e-mail, with a copy to the REC operational manager. It is the operational manager’s responsibility to investigate further and ensure that the outcome of the SSA is notified as quickly as possible.

4.47 Where the SSA REC has no objections to the research on site-specific grounds, the Coordinator of the main REC should be notified electronically using RED. Where for any reason RED cannot be used, the SSA REC should notify the main REC by e-mail (SL19 may be used).

4.48 Where the SSA REC has objections on site-specific grounds, the Coordinator should write to the main REC by e-mail using SL20, giving specific reasons for the objections.

4.49 The SSA REC should not copy the advice given to the main REC to the Principal Investigator, as there may need to be further discussion with the main REC about any issues arising (see paragraphs 4.64). The Principal Investigator will be notified of the outcome in due course once the main REC has informed the Chief Investigator (see paragraph 4.60).

4.50 Where the SSA REC has any concerns about the research that are not directly relevant to the SSA, it may separately refer these to the main REC in writing. The SSA REC should not, however, delay the SSA or raise formal objection to the research being conducted at the site on the basis of these concerns. It is entirely a matter for the main REC to consider any matters that are raised in this way as part of the process of ethical review.

4.51 SSA is a documentary check, supplemented where necessary by discussion with the Principal Investigator where the SSA REC requires additional information or clarification. It is not normally necessary for the SSA REC to visit a site for the purpose of trial-specific SSA, especially where it is already familiar with the site and

Site visits

4.51 SSA is a documentary check, supplemented where necessary by discussion with the Principal Investigator where the SSA REC requires additional information or clarification. It is not normally necessary for the SSA REC to visit a site for the purpose of trial-specific SSA, especially where it is already familiar with the site and
the type of research it undertakes. However, the SSA REC has the discretion to arrange a site visit. This might be appropriate for the purpose of the SSA where the study involves significant risk to participants, the site is unfamiliar and a visit is considered essential to gain an understanding of the context in which the research will be undertaken and assess the suitability of the staff and facilities.

4.52 Where the site is a specialist research unit with which the SSA REC is already familiar, it may be helpful to arrange occasional visits to maintain the Committee’s knowledge of the site, facilities, key personnel and operating procedures. The frequency of visits is at the discretion of the SSA REC. As a guideline, annual visits might be appropriate. It is for the SSA REC to determine which members should be involved.

**Accreditation of Phase 1 trial sites by the MHRA**

4.53 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 at: [http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm](http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm).

4.54 Trial-specific SSA for Phase 1 trial sites should take the accreditation status of the site into account. It is not necessary for the SSA to review issues routinely addressed by the GCP inspectors as part of the process leading to accreditation. The inspectors will notify the designated SSA REC 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. Any critical findings identified during inspection will be promptly notified to the SSA REC so that these can be taken into account in any SSAs undertaken prior to the issues being resolved and accreditation confirmed.

**Review of general advertising and screening procedures at clinical trial units**

4.55 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, trial units may seek ethical advice on the procedures on a voluntary basis. Requests for advice should be submitted in writing to the designated SSA REC for the site, enclosing relevant documentation such as advertising material or screening protocols. The request should not form part of either the main application or a SSA application relating to a particular trial. The SSA REC has the discretion to review the proposed procedures, although it is not obliged to do so. The review should be undertaken by a sub-committee or at a meeting of the Committee. The SSA REC may provide ethical advice and, if appropriate, give its approval to the proposed procedures. Any such
approval should be given separately to the favourable opinion letter for a particular trial.

**Action by the main REC following SSA for a non-NHS site**

4.56 Following notification of the outcome of the site-specific assessment, the main REC should proceed as follows.

**No objection on site-specific grounds**

4.57 No non-NHS sites should be approved by the main REC until it is in a position to give a favourable ethical opinion to the application.

4.58 When giving a favourable ethical opinion for any study requiring SSA, the main REC should at the same time give specific approval for all non-NHS sites for which notification of no objection has so far been received from the SSA REC or where the SSA is carried out by the main REC alongside the ethical review. Approved sites should be listed in the favourable opinion letter (SL5 or SL14 as appropriate).

4.59 Where the main REC is not a REC for one of the research sites, there may be occasions when it is in a position to issue a favourable opinion but no SSA has yet been notified by another REC. The Co-ordinator should investigate the reasons why:

- If RED shows that no SSA has yet been submitted, it may be necessary to advise the Chief Investigator about the procedures.
- If one or more SSAs have been submitted but the outcome is overdue, the Co-ordinator should follow this up with the SSA REC concerned or with the REC operational manager (see paragraph 4.46).

In the meantime the favourable opinion letter (SL5 or SL14) should be issued to the Chief Investigator without delay in all cases. (The letter should make it clear the study cannot start at any non-NHS site.) As soon as one or more SSAs for non-NHS sites have been notified with no objection, approval for these sites should be confirmed by sending SL23C to the Chief Investigator, copied to the sponsor’s contact point.

4.60 It is the responsibility of the Chief Investigator to notify the Principal Investigator at each non-NHS site that the study has a favourable ethical opinion and approval for the site, and for the Principal Investigators then to seek final approval to proceed from the host organisation.

4.61 Where, following the issue of a favourable ethical opinion, a further notification of no objection for a site is received from a SSA REC, the main REC should confirm the favourable opinion for the new site by issuing SL23C to the Chief Investigator, copied to the sponsor.

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**Objection on site-specific grounds.**
4.62 Where the main REC is notified of objections to the research on site-specific grounds, the Chair should consider the objections, in consultation with other members as necessary, and decide on behalf of the REC whether to issue an unfavourable opinion for the site. The normal presumption is that an unfavourable opinion will be issued unless paragraph 4.63 or 4.64 applies. The Chief Investigator should be advised of the reasons for an unfavourable opinion using SL23.

4.63 The main REC may contact the SSA REC to request further information about the reasons for the objections if it considers this necessary, for example if it appears that the objections are not site-specific or that they may be based on a misunderstanding of the research. The main REC has the authority to over-rule the objections and issue a favourable opinion if it is satisfied that there is no valid objection to the research being conducted at the site concerned. The SSA REC and the REC operational manager with responsibility for the SSA REC should be notified in advance, and it may be helpful for the main REC to discuss the issues with the Chair of the SSA REC and explain the reasons for the decision.

4.64 If the SSA REC notifies the main REC of objections, and information is subsequently received from the Principal Investigator that resolves the issues causing concern, the SSA REC should contact the main REC as soon as possible to explain that the objections no longer apply. After any necessary discussion with the SSA REC, and assuming it is satisfied with the new advice, the main REC should write to the Chief Investigator to explain that approval for the site can now be given.

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Representations by the Chief Investigator

4.65 Where the main REC issues an unfavourable opinion for a research site, there is no formal process of appeal. However, the Chief Investigator may make representations in writing to the main REC. Any such representations should be given due consideration by the main REC (in consultation with the SSA REC as appropriate). The Chief Investigator should not be permitted to approach the SSA REC directly.

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Revision of the main application with implications for SSA

4.66 Where the Chief Investigator revises the main application during the ethical review, the information given to SSA REC in the SSI form may no longer be complete or accurate. In such cases, the main REC should consider the following options:

- Where the revisions are ethically acceptable but in the judgement of the main REC the implications for site-specific assessment are minor (e.g. modification of the schedule of study procedures), any SSAs already underway should continue.
- Where the revisions are ethically acceptable but could have significant implications for the site-specific assessment (e.g. addition of new study procedures requiring special facilities), the Chief Investigator may be required to
notify all SSA RECs of the changes in writing. Alternatively, the main REC may contact SSA RECs directly. Where the SSA is still underway, the SSA REC should take the changes into account in making its assessment and may seek further information from the Principal Investigator. Where the SSA has already been completed and the outcome notified to the main REC, the SSA REC should review its assessment and notify the main REC if it now has any site-specific objection.

- Where the revisions are not ethically acceptable, the main REC should give an unfavourable opinion (see paragraph 4.67 and section 7).

Unfavourable opinion on the main application

4.67 Where the main REC issues an unfavourable opinion on the main application, RED will alert all SSA RECs that have received, or subsequently receive, applications for SSA. Any SSA that is underway should be discontinued. Section 7 describes procedures for further review following an unfavourable opinion, including SSA where applicable.

Delegation of SSA to another body

4.68 The REC operational manager may make arrangements for SSAs relating to a particular site or sites to be delegated to another local body with expertise in the management of health-related research. The terms of the delegation should be set out in a written agreement, which should be approved by the NRES Head of Operations. The REC system remains accountable for the process of site-specific assessment and for the provision of appropriate advice on the outcome of the SSA to the main REC within 25 days.

4.69 The agreement between the REC operational manager and the assessment body should include provision for the following:

- Definition of the research site(s) and/or geographical area covered by the agreement;
- Procedures for referral of valid applications for SSA to the assessment body by the SSA REC Co-ordinator;
- All SSAs to be reviewed by at least two assessors, including an individual of appropriate seniority;
- Compliance with the guidance in paragraph 4.39 on the issues to be considered in the SSA, with no consideration of any other issues;
• The outcome of SSAs to be notified to the SSA REC Co-ordinator in writing within 25 days of the receipt of the valid application (or 14 days in the case of a Phase 1 trial);

• The SSA REC Co-ordinator to retain responsibility for notifying the outcome of the SSA to the main REC and for use of RED;

• There may be further discussion of the SSA directly between the main REC and the assessors, in particular where the main REC is considering over-ruling objections, but the SSA REC and the REC operational manager should be kept informed (see paragraph 4.63);

• Monitoring of the agreement by the REC operational manager, with a formal review at least annually.

Addition of new sites and Principal Investigators

4.70 Procedures for extension of a study to new sites, appointment of new Principal Investigators or other site-specific amendments are set out in paragraphs 5.64-5.82.

Closure of sites

4.71 In a study requiring SSA, the Chief Investigator or sponsor should notify the main REC where an approved site is closed or withdrawn from the study prematurely, for example if the care organisation withholds research governance approval, or the Principal Investigator withdraws from the study, or the sponsor decides that the site is no longer suitable. The SSA REC for a non-NHS site should also be notified. Notification may be made by letter. A Notice of Substantial Amendment is required only for a temporary halt at a study site to protect participants from harm (see paragraph 5.30).

4.72 There is no requirement for the Chief Investigator or sponsor to notify the main REC of the routine closure of active sites at the conclusion of a study.

Monitoring of research sites

4.73 Operational policy on the monitoring of research is set out in section 9. In general, the main REC is not responsible for proactive monitoring of research. However, it has a duty to keep the favourable ethical opinion under review in the light of progress reports and significant developments, and may review the opinion at any time.

4.74 Neither the main REC nor the SSA REC is responsible for proactive monitoring of the conduct of the research at individual sites. However, where information comes to the attention of either REC that raises questions about the suitability of the site or investigator, the favourable opinion for the site may be reviewed. Procedures for review of opinions and for suspension or termination of opinions in non-CTIMPs are set out in paragraphs 9.80-9.87. Only the main REC has authority to suspend or terminate an opinion whether for the study as a whole or an individual site.
4.75 Where concerns are drawn to the attention of the SSA REC, it may review the original site-specific assessment or request further advice from a delegated assessor. The SSA REC or delegated assessor may seek further information from the Principal Investigator and/or request submission of a new SSI Form or CV if necessary. If it is not possible to resolve the concerns, the SSA REC should bring them to the attention of the main REC as soon as possible. The REC operational manager should be notified.

4.76 The main REC may request a new SSA at a particular site at any time in the light of concerns brought to its attention from any source. It may do so either by writing to the Chief Investigator, requiring formal submission of a new application for SSA, or by writing directly to the SSA REC.

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Amendments to multi-site research

4.77 Procedures for reviewing amendments to multi-site research are set out in Section 5, including extension to additional sites (paragraphs 5.67-5.76), appointment of new Principal Investigators (paragraphs 5.77-5.80) and site-specific protocol amendments (paragraphs 5.81-5.83).

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Section 5: Amendments to research given a favourable opinion

Summary

The Clinical Trials Regulations define a “substantial amendment” as one that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects 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.

Substantial amendments may include changes to the terms of the REC application, the protocol or any other supporting documentation for the trial.

It is the sponsor’s responsibility to decide what is substantial, though the REC may give advice if requested.

The sponsor of a CTIMP must notify a substantial amendment to the MHRA and/or the main REC, depending on the type of amendment. Annex C gives guidance on responsibilities for review of amendments. Some amendments require both authorisation from the MHRA and a favourable opinion from the REC.

For non-CTIMPs, the same definition of a “substantial amendment” applies and a favourable opinion from the main REC is always required before implementation.

“Minor” (or “non-substantial”) amendments may be made at any time. There is no requirement to notify the main REC or obtain an ethical opinion.

Substantial amendments to CTIMPs should be notified using the European Commission notice of substantial amendment form. For other research the NRES form should be used. Both forms are available within IRAS.

Reasons for the changes should be fully explained and amended documentation provided. Notice of Substantial Amendment (or any modified amendment) must be authorised or co-authorised by a representative of the sponsor.

The main REC has 35 days from receipt of a valid notice of amendment to give an opinion. The clock does not stop during this period. Amendments may be reviewed in sub-committee or at a full Committee meeting, but not by the Chair acting alone.

If an unfavourable opinion is given, the sponsor or Chief Investigator may modify the amendment. The REC should give an opinion on a modified amendment within a further 14 days. Responsibility may be delegated to the Chair. If an unfavourable opinion is given the applicant may submit a further modified amendment taking account of the REC’s concerns.

The applicant may appeal following an unfavourable opinion on a substantial amendment or modified amendment. The amendment will then be reviewed again at a full meeting of the REC, taking into account the applicant’s representations and the opinion of another REC.

For studies involving site-specific assessment (SSA), substantial amendments at individual sites require an application for SSA in the normal way. This includes the addition of a new site or appointment of a new local Principal Investigator. (If it is a CTIMP a notice of amendment should also be submitted to the main REC for sites not previously notified.) The main REC will give an opinion on the new site or PI following SSA.
Amendments to the study as a whole do not require SSA but the main REC may make site-specific approval conditions or seek further advice from local RECs. Guidance is given on proposed amendments that may warrant a new application. Urgent safety measures may be taken to protect participants from an immediate hazard to their welfare or safety. The main REC must be notified within 3 days.
Statutory requirements

5.1 Under the Clinical Trials Regulations, the sponsor of a clinical trial of a medicinal product may make an “amendment to a clinical trial authorisation”, other than a “substantial amendment”, at any time after the trial has started. Amendments that are not substantial (referred to in these SOPs as “minor amendments”) do not need to be notified. Where the amendment is substantial, the sponsor is required to submit a valid notice of amendment 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 amendments.

5.2 An “amendment to a clinical trial authorisation” is defined broadly in the Clinical Trials Regulations as an amendment 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

any other particulars or documents submitted with the applications to the MHRA or the main REC.

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

(a) the safety or physical or mental integrity of the subjects 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.

5.4 Under the EU Directive the European Commission has issued guidance on amendments as part of the “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of a trial” (ENTR/CT1). Annex 2 to the guidance prescribes a Notification of Amendment form (“the EU Notification of Amendment”) to be used in all member states for notification both of the competent authority and the ethics committee. The sponsor must indicate on the form whether the amendment requires authorisation by the competent authority, or a favourable opinion from the ethics committee, or both.

5.5 Where the sponsor requests an ethical opinion on a CTIMP, this should be given in all cases within 35 days of receiving a valid notice of amendment.

5.6 If the opinion is unfavourable, the sponsor may then modify the proposed amendment. A written notice of the modification should be sent to the main REC at least 14 days before it is due to be implemented. The REC may then give an
unfavourable opinion on the modified amendment within 14 days, otherwise it may be implemented.

5.7 Amendments 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

5.8 The policy of the UK Health Departments is that the statutory provisions relating to substantial amendments to CTIMPs should generally apply to the review of substantial amendments to any research study that has previously been ethically approved by 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 amendments, except those proposing to include adults lacking capacity for the first time in a non-CTIMP, where 60 days is allowed for the review and the clock may be stopped once to request further information or clarification (see paragraph 12.61).

5.9 Substantial amendments 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 amendments

Notification before the commencement of the research

5.10 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 amendment, it should be notified and reviewed in the same way as a substantial amendment after the study has started.

5.11 A Notice of Substantial Amendment form may exceptionally be submitted with or during the initial application for ethical review. This might be necessary for example where the research is being reviewed in parallel by another UK regulatory body (e.g. the MHRA) and significant changes need to be made as a result of that review. It could also 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 amendment to regulatory authorities and ethics committees in each country. In these circumstances it is acceptable for a Notice of Substantial Amendment form to be included as part of the initial application package or submitted during the review process. If the REC’s
opinion is favourable, the amendment 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 amendment. However, if the amendment is submitted during the ethical 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 days of receiving the amendment.

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Notices of amendment

5.12 For CTIMPs, the EU Notification of Substantial Amendment form should be used (see paragraph 5.4). In accordance with the European Commission guidance, the form may be submitted by the sponsor, the sponsor’s legal representative, the Chief Investigator, or another person or organisation authorised by the sponsor.

5.13 For all other research, the NRES Notice of Substantial Amendment form should be used. The form may be submitted by either the sponsor or the Chief Investigator, but should always be authorised by both the Chief Investigator and a representative of the sponsor.

5.14 In all cases, the Notice of Substantial Amendment (or any modified amendment) should summarise the change(s) included in the amendment and briefly explain the reasons in each case or refer to supporting documentation explaining the changes. One notice of amendment may refer to a number of different changes. The form should be completed in language comprehensible to a lay person.

5.15 All notices of amendment should be submitted to the main REC electronically from IRAS\(^\text{13}\), together with the documents that have been modified, showing both the previous and the new wording. Where the modified documents (for example the study protocol) are lengthy and the changes are not so widespread or significant as to justify a new version, 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.

5.16 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 amendment 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.

\(^{13}\) See paragraph 11 of the Introduction to the SOPs in relation to implementation of arrangements for electronic submission.
Validation of notice of amendments

5.20 The period of 35 days, within which an ethical opinion must be given, normally begins when a valid notice of amendment is received by the main REC. (However, special procedures apply where the amendment requires an application for SSA — see paragraph 5.63.)

5.21 The relevant date (“the validation date”) is the working day on which the notice of amendment and all supporting documents are received by the REC in RED.

5.22 A notice of amendment should be accepted as valid if all the following criteria are met:

(a) The relevant notice of amendment form has been completed in full, including the sponsor’s amendment number, and submitted electronically from IRAS\(^\text{14}\).

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

(c) The notice of amendment has been electronically authorised by the named applicant on behalf of the sponsor (CTIMPs); or by the Chief Investigator and the sponsor’s authorised representative (non-CTIMPs)\(^\text{15}\).

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

(e) Where the amendment proposes to include adults lacking capacity in the research for the first time, the additional documents listed in paragraph 12.60 should be submitted.

(f) Where the amendment seeks Section 34 approval under the Mental Capacity Act 2005, the additional documents listed in paragraph 12.37 should be submitted, and the study must have started prior to 1 October 2007 (see paragraph 12.15).

(g) Where the amendment proposes to increase the exposure of participants to ionising radiation, or to include such exposure for the first time, Part B Section 3 of the REC application form in IRAS should be submitted.

5.23 It is the responsibility of the Co-ordinator of the main REC to decide whether or not the notice of amendment is valid and to notify the sponsor and Chief Investigator using SL27 (valid notice) or SL28 (invalid notice). Notification should normally be given within 5 working days of receipt, except that there is no need to issue a validation letter if the sub-committee is able to review the amendment and reach an opinion within 5 working days. (Where the amendment relates solely to the addition

\(^{14}\) Exceptionally, Co-ordinators have discretion to accept submission of the notice of amendment and/or supporting documentation in another electronic format (e.g. by email or on CD) where the applicant is unable to submit from IRAS due to technical problems with the system and the submission is urgent.

\(^{15}\) See footnotes to paragraph 1.45(d)
of a new site or investigator in a CTIMP, special procedures apply – see paragraph 5.67.)

5.24 Where the notice is sent to another REC in error, the Co-ordinator should notify the Chief Investigator as soon as possible that it should be re-submitted from IRAS to the main REC. The validation date will be the working day on which the main REC receives the documentation in RED.

5.25 The decision whether or not a notice of amendment is valid should normally be made by the REC Co-ordinator. The agreement of the Chair is not required.

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Deciding whether an amendment is substantial

5.26 For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial. Any valid amendment submitted as a substantial amendment should be accepted for review. Equally, if the sponsor is satisfied that an amendment is not substantial, there is no requirement to notify the REC although non-substantial amendments may be notified for information only at the sponsor’s discretion (see paragraph 5.37).

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5.27 Sponsors and CIs may seek advice from REC offices or the NRES Queries Line on whether an amendment should be considered substantial. Co-ordinators may give advice in straightforward cases, or may seek advice from the operational manager or the Chair. When giving advice, it should always be made clear that it is ultimately the sponsor’s responsibility to determine whether an amendment is substantial.

5.28 For CTIMPs, sponsors should be referred initially to the current guidelines from the European Commission in the “Detailed guidance for the request for authorisation of a clinical trial, on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” (CT1, revision 3, March 2010) at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm. The sponsor may seek further advice at their discretion.

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

5.30 Guidance from NRES is that the following changes should normally be regarded as substantial:
• 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
• A change of sponsor(s) or sponsor’s legal representative
• Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a CI
• In a CTIMP, addition of a new site not listed in the original application
• In a non-CTIMP requiring SSA, addition of a new non-NHS site not listed in the original application (but note the procedural guidance in paragraphs 5.72-5.74)
• 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 site to protect participants from harm, and the planned restart of a study following a temporary halt (see paragraph 9.76-9.78)
• Early closure or withdrawal of a site (see paragraph 4.71)
• A change to the definition of the end of the study (see paragraph 9.81)
• Any other significant change to the protocol or the terms of the REC application.

5.31 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 can be regarded as non-substantial or minor amendments. Examples might be as follows:
• Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications
• Changes to the Chief Investigator’s research team
• Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator)
• In a non-CTIMP, addition of any new NHS site, or addition of a non-NHS site in a study not requiring SSA (see paragraphs 5.72-5.74)
• Routine closure of sites at the end of the study
• Changes in funding arrangements
• Changes in the documentation used by the research team for recording study data
• Changes in the logistical arrangements for storing or transporting samples
• Extension of the study beyond the period specified in the application form (see paragraph 9.10)
• Issue of an updated Investigator’s Brochure or Summary of Product Characteristics relating to an investigational medicinal product.

5.32 Changes to contact details for the sponsor (or the sponsor’s representative), Chief Investigator or other project staff are minor amendments but it is recommended they are but should notified to the main REC for information.

5.33 For further guidance on procedures for addition of new sites, appointment of new Principal Investigators and other site-specific amendments, see paragraphs 5.67-5.83.

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Substantial amendments to CTIMPs – authorisation or ethical opinion?

5.34 It is the responsibility of the sponsor to decide whether a substantial amendment requires authorisation, or an ethical opinion, or both. However, sponsors may wish to take account of the general guidance in Annex C, which has been agreed between NRES and the MHRA and takes account of the guidance from the European Commission (see paragraph 5.28 above).

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Substantial amendments to CTIMPs notified for information only

5.35 Where a substantial amendment to a CTIMP requires authorisation by the MHRA only, there is no requirement to notify the main REC. Where it is notified voluntarily, the Co-ordinator should acknowledge receipt within 30 days by sending SL29 to the sponsor (or other person submitting the notice on behalf of the sponsor).

5.36 The amendment 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 amendment could affect the ethical 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 ethical opinion should have been requested and making any comment on ethical issues raised by the amendment. A REC may review its opinion of a study at any time and may suspend or terminate a favourable opinion if serious concerns arise (paragraphs 9.87-9.92). Although in the case of a CTIMP it is primarily for the sponsor to interpret the guidance on the need for ethical review of amendments, the REC may review any information it receives.
Notification of minor amendments

5.37 Where changes are made to a research study that the sponsor considers minor rather than substantial amendments, there is no requirement to obtain an ethical opinion. They may be notified to the main REC for information, and this may be helpful where the change relates to the contact details for the study or involves minor clarifications or updates to the information sheet or consent form for participants. Where minor amendments are notified, the sponsor or Chief Investigator should do so by letter rather than by submitting a notice of amendment form. It is helpful if the letter states clearly that the amendment is not considered to be substantial and an ethical opinion is not required.

5.38 Minor amendments do not need to be reported to the Committee. The Co-ordinator should acknowledge receipt of any minor amendment within 35 days using SL30 (CTIMPs) or SL31 (non-CTIMPs). Referral of minor amendments to the Chair or other members for information is at the discretion of the Co-ordinator.

5.39 Where a sponsor or Chief Investigator notifies the main REC of a minor amendment, but the Chair considers that it should have been regarded as substantial and requires ethical review, the matter may be discussed at a meeting of the sub-committee or Committee. A REC may review its opinion of a study at any time (paragraph 9.87-9.102). Although in the case of a CTIMP it is primarily for the sponsor to interpret the guidance on what is substantial, the REC may review any information it receives.

Review of substantial amendments

5.40 Except where paragraphs 5.44 or 5.46 apply, substantial amendments should be reviewed by a sub-committee of the main REC (see Section 6) or by the Committee itself. They may not be reviewed by the Chair acting alone, except where the Chair has been given delegated authority at a meeting to review a modified amendment (see paragraph 5.4649).

5.41 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 amendment.

5.42 The decision reached should be either a favourable or unfavourable opinion of the amendment. It is not permitted to give a favourable opinion for part of the amendment only. However, when giving an unfavourable opinion the REC may indicate which parts of the amendment would have been acceptable and give guidance on the submission of a modified amendment taking account of its concerns. The Co-ordinator should notify the sponsor and Chief Investigator of the decision using one of the following letters:

SL32 Favourable opinion of substantial amendment
Unfavourable opinion of substantial amendment

The opinion letter should include the same information that would be included in an opinion letter on a new application (see paragraph 3.15), including a contact point for receipt of queries from the applicant.

In the case of CTIMPs, the main REC is required by the Clinical Trials Regulations to notify the MHRA of its opinion on the substantial amendment, whether favourable or unfavourable, so that it can be entered on EudraCT. The MHRA is notified automatically of all opinions on substantial amendments and modified amendments through its access to RED. Where the MHRA has been asked to authorise a substantial amendment, it will issue a written notice within 35 days accepting the amendment or giving grounds for non-acceptance. It is the responsibility of the sponsor to arrange for the main REC to be provided with a copy of the notice for information.

Where a substantial amendment relates solely to the addition of a new site, appointment of a new Principal Investigator or other changes to the management or conduct of the study at a particular site, the procedures in paragraphs 5.67-5.83 should be followed. There is no requirement for the amendment to be formally reviewed by the Committee or sub-committee of the main REC. Site-specific amendments to the protocol, participant information sheet or other study documentation should be reviewed by the main REC according to normal procedures.

Further information or clarification from the applicant

The 35 day clock does not stop pending receipt of any further information or clarification requested by the REC relating to a substantial amendment, except where paragraph 12.61 applies. If time allows, however, the REC may invite the sponsor or Chief Investigator to provide further information or clarification in writing by a specified date within the period of 35 days allowed for the review. If the further information is not provided by this date, or is incomplete or unsatisfactory, the amendment may be rejected.

The applicant may be invited to submit a modified amendment taking account of the REC’s concerns. The Committee or sub-committee may delegate responsibility to the Chair to give a favourable opinion of the amendment if it is subsequently modified in a way that meets all the concerns of the REC. Procedures for reviewing modified amendments are set out in paragraphs 5.48-5.53.

Where it appears that the amendment may significantly affect the scientific value of the trial, for example because it modifies the recruitment targets, the selection criteria or the data analysis, the REC may require that the applicant provides evidence of further scientific review in support of the amendment.
Modified amendments

5.48 Where the REC gives an unfavourable opinion of a substantial amendment, the sponsor or Chief Investigator may submit a modified amendment taking account of the Committee's concerns. The notice of amendment form should be re-submitted, amended as necessary, and should be accompanied by any supporting documents that have been modified. The form should be clearly marked to indicate that it relates to a modified amendment.

5.49 The amendments may be divided into more than one modified amendment to allow for separate opinions to be given on each part of the package.

5.50 A notice of a modified amendment should be submitted to the main REC at least 14 days before it is planned to implement the amendment.

5.51 The Co-ordinator should make arrangements for a modified amendment to be reviewed as soon as possible. It should be reviewed by a sub-committee or, if authority has previously been delegated under paragraph 5.48, by the Chair. The REC should give either a favourable or unfavourable opinion. The Co-ordinator should notify the sponsor and Chief Investigator of the decision of the REC within 14 days of the receipt of the modified amendment, using either SL34 (favourable opinion) or SL35 (unfavourable opinion).

5.52 Decisions on modified amendments taken by the Chair under delegated authority should be reported to the Committee in the Co-ordinator's report.

5.53 Where an unfavourable opinion is given on a modified amendment, the sponsor or Chief Investigator may submit a further modified amendment taking account of the REC's concerns. Alternatively, they may appeal (see paragraph 5.54).

Appeals

5.54 There is no statutory provision for appeal against a decision of the main REC to give an unfavourable opinion of a substantial amendment. However, an applicant may request leave to appeal by writing to the relevant Appeal Manager for the REC concerned (see paragraph 7.19) within 90 days of the date of the opinion letter, setting out representations with respect to the opinion. Leave to appeal will normally be granted, though the Appeal Manager has the discretion to refuse leave where there are no reasonable grounds for appeal. The Chair of the main REC should be notified of the receipt of the appeal.

5.55 Where leave to appeal is accepted, the Appeal Manager should arrange for the amendment 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 main REC, copied to the Appeal Manager, within 14 days.

5.56 Where it could be helpful to the main REC in reviewing the appeal, the Appeal Manager may also seek advice from other referees; draw the attention of the main REC to published guidance, including guidance from the National Research Ethics
Advisers’ Panel; or arrange for further guidance to be provided on issues of law, regulation or operational procedure.

5.57 Once all external comments and additional guidance have been provided, the Co-ordinator of the main REC should submit the amendment documentation, together with the applicant’s representations, for re-review at the next full meeting of the main REC. The sponsor’s representative and Chief Investigator should be invited to attend the meeting to make further oral representations and be available to answer questions.

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

(a) Favourable opinion

(b) Provisional opinion, indicating support for the amendment in principle but requesting further information or a modified amendment before a favourable opinion can be given

(c) Unfavourable opinion.

The decision should be communicated to the applicant in writing within 5 working days of the meeting.\(^{16}\)

5.59 The main REC remains fully responsible for the opinion, and may confirm its original unfavourable opinion if it continues to believe that the amendment 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.

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### Amendments requiring submission of a new application

5.60 A proportionate approach should always be adopted in assessing whether a new application, rather than an amendment, is required. A new application should only be required where a proposed amendment 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 amendment 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 classes of investigations or other interventions (rather than simply re-scheduling or modifying those already approved);

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\(^{16}\) Standard letters for these decisions will be developed and made available to the Co-ordinator by the Appeal Manager as required.
• Recruitment of a new type of participant (especially if these would be regarded as being from vulnerable groups);
• A proposed sub-study with a different Chief Investigator and/or an intention to publish the results separately from the parent study.

Where a REC requests submission of a new application, it should give reasons to the applicant with reference to these criteria.

5.61 Where an amendment involves the submission of a separate protocol, the REC should normally require the submission of a new application.

5.62 Where a REC requests submission of a new application and the study is a CTIMP, the REC should first consult the MHRA Clinical Trials Unit to agree a common position on the matter.

5.62A Where the concerns with a proposed amendment arise solely from the apparent complexity and extent of the changes, the REC should give consideration to reviewing the Notice of Substantial Amendment at a meeting of the full committee and inviting the Chief Investigator and/or sponsor’s representative to attend (see paragraphs 5.40-5.41).

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Amendments to multi-site studies

5.63 In general there is no requirement for other RECs to be informed of protocol amendments to multi-site studies. In most cases, protocol amendments will not have significant ethical implications for the suitability of individual sites to conduct the study. (For amendments relating to particular sites, see paragraphs 5.67-5.77.)

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

5.65 Where, exceptionally, the main REC considers that the proposed changes to the study could have significant ethical implications for the suitability of sites, it should first consider the guidance in paragraph 5.60. It may well be that a new application is required for the study as a whole in such cases.

5.66 Where the main REC considers it reasonable to give a favourable opinion on the amendment without a new application, but remains concerned about possible ethical implications at individual sites, it should proceed as follows:
• The favourable opinion should be issued to the applicant within 35 days.
• New SSAs at non-NHS sites should not be requested before issuing the opinion, as the 35 day time limit allows insufficient time for this process.
• The main REC should consider attaching conditions to a favourable ethical opinion, relating to implementation at local sites. For example, the opinion might be given on the assumption that the amendment will not be implemented at any
site 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 site. The responsibility would then lie with the sponsor and the care organisation to ensure that it was reasonable for the amendment to be implemented.

- Exceptionally, the main REC may also write directly to SSA RECs for non-NHS sites by letter or e-mail, explaining the specific concerns of the main REC about the potential local implications of the amendment. (A copy of the amendment should be enclosed, or the main REC may summarise the relevant points.) This may be for information only, or RECs may be asked to review a particular aspect of the SSA and to advise the main REC by a specified date whether it has any concerns about the continued suitability of the site.

- The Chair of the REC should consider any such request and respond in writing on behalf of the REC. Other members may be consulted if appropriate. Further information may be sought from the Principal Investigator.

- In the light of any site-specific objections raised by a SSA REC, the main REC may review the favourable opinion for a non-NHS site at any time (see paragraph 9.87-9.102).

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Amendments relating to individual sites

CTIMPs

5.67 The inclusion of a new site (not listed as a planned site in the original application), appointment of a new Principal Investigator or any other significant change to the management or conduct of the trial at a particular site is a substantial amendment, requiring notification to the main REC and the MHRA on the European Commission Notice of Substantial Amendment Form. The REC should give an opinion within 35 days of receipt of a valid notice of amendment (see paragraph 5.71).

5.68 Where the amendment relates only to NHS site(s), the Co-ordinator should issue SL23B within 5 working days, confirming a favourable opinion on condition that permission is given or continued by the R&D office(s) for the care organisation(s) involved. New sites should be manually added to the list of approved sites in RED. Responsibility for SSA lies with the NHS care organisation. It is not necessary for the amendment to be reviewed or notified to the Committee. If any doubt arises whether the site(s) concerned are NHS sites, the Co-ordinator should seek clarification from the sponsor and/or the care organisation concerned.

5.69 Where the amendment includes any changes at non-NHS sites, the responsibility for SSA lies with the REC system. The Co-ordinator should validate the amendment in the normal way. If the amendment is valid, SL23A should be sent within 5 working days of receipt. The sponsor should arrange for the Principal Investigator to apply for
SSA by submitting the SSI Form and accompanying documentation in the normal way.

5.70 Following SSA for a new non-NHS site, the main REC should issue an opinion using either SL23C (favourable opinion) or SL23 (unfavourable opinion).

5.71 The main REC should not issue the opinion until it has received both the Notice of Substantial Amendment form and the outcome of the SSA. Co-ordinators should note that the validation date for an amendment relating to a non-NHS site is the date by which both a valid Notice of Substantial Amendment form has been received by the main REC and a valid application for SSA has been received by the SSA REC. If only the outcome of the SSA is received, the Co-ordinator should contact the sponsor to request that the notice of amendment be provided. When the notice of amendment is received, the opinion should be issued.

Other studies requiring SSA

5.72 The sponsor may extend the study to additional NHS sites, subject to obtaining permission from the NHS R&D office prior to starting the research at the site. Site-specific assessment is undertaken by the NHS R&D office as part of the research governance review. There is no requirement for the main REC to be notified of the new site. The site is deemed to be approved within the terms of the favourable opinion for the study from the main REC.

5.73 Where the study is to be extended to a new non-NHS site, specific approval for the site is required from the main REC. An application for site-specific assessment should be made to an appropriate REC and processed in the usual way (see paragraphs 4.30-4.38).

5.74 There is no requirement to submit a Notice of Substantial Amendment form to the main REC, either for NHS or non-NHS sites.

Research not requiring SSA

5.75 The sponsor may extend the study to additional NHS and non-NHS sites, subject to obtaining permission from the NHS care organisation or other organisation responsible for participants at the site. There is no requirement for the main REC to be notified of the new site(s) or for application to be made for SSA. The site(s) are deemed to be approved within the terms of the favourable opinion for the study from the main REC.

5.76 There is no requirement to submit a Notice of Substantial Amendment form to the main REC, either for NHS or non-NHS sites.

Appointment of a new Principal Investigator at a site

5.77 The appointment of a new Principal Investigator at a site in a CTIMP is a substantial amendment, requiring a favourable opinion from the main REC. The procedures set out in paragraphs 5.67-5.71 should be followed. The trial should normally continue at
the site but, if no Principal Investigator is in place, no new participants should be recruited until a favourable opinion has been given and, in the case of NHS sites, permission for the new Principal Investigator has been given by the R&D office.

5.78 Other changes to the local research team at individual sites are not regarded as substantial amendments. At the discretion of the Principal Investigator they may be notified to the SSA REC for a non-NHS site by letter for information only.

5.79 There is no requirement to notify the main REC of the appointment of a new Principal Investigator or Local Collaborator in a non-CTIMP requiring SSA. At NHS sites, the R&D office should be notified of the appointment and continued permission sought. In the case of a non-NHS site, the SSA REC should be notified and a copy of the CV for the new PI provided. The SSA REC should review the CV in sub-committee. If it has any concerns about the appointment, it should notify the main REC.

5.80 There is no requirement to notify the main REC of the appointment of a new Principal Investigator or Local Collaborator in a study not requiring SSA. At NHS sites, the R&D office should be notified and continued permission sought.

Site-specific amendments to the protocol or participant information

5.81 In multi-site studies it may be necessary for site-specific amendments to be made to the research procedures in the protocol or to study documentation such as the participant information sheet. Where such amendments meet the criteria for minor amendments (see paragraph 5.31), the sponsor may authorise the amendment without notifying the main REC or seeking an ethical 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.

5.82 Where a site-specific amendment is substantial, a Notice of Substantial Amendment form should be submitted to the main REC for review according to normal procedure. Guidance on the consideration of site-specific issues is given in paragraph 5.66.

5.83 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 main 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 site. Where appropriate, the generic participant information sheet may include text options to be selected by the local Principal Investigator, depending on local practice. The main REC should then consider whether such variation is permitted within the terms of the single ethical opinion for the study.

Appointment of a new Chief Investigator
5.84 The appointment of a new Chief Investigator is a substantial amendment, requiring a favourable opinion from the main REC. In addition to the notice of amendment, the applicant should submit:

- A copy of the new Chief Investigator’s CV
- The Declaration sheet in Part D of IRAS, signed by the new Chief Investigator.

5.85 If the new Chief Investigator will also be appointed as a new local Principal Investigator at a research site, this should be made clear on the notice of amendment form. If it is a NHS site, the R&D office should be notified. If it is a non-NHS site in a study requiring SSA, the SSA REC should be notified. It is not necessary for a further SSA to be carried out but if the SSA REC has any concerns about the appointment of the new PI it should inform the main REC.

Absence of Chief or Principal Investigator

5.86 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.

5.87 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 recommended that an acting or new CI or PI should be appointed (see paragraphs 5.67-5.71, 5.77-5.80 and 5.84-5.85.)

- 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 main REC should be notified by letter about cover arrangements for absent CIs. R&D offices at NHS sites should be notified about cover arrangements for absent PIs. For non-NHS sites in studies requiring SSA, the SSA REC should be notified. If it has any concerns about the suitability of the arrangements, it should notify the main REC. The main 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 main REC or SSA REC.

5.88 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.

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Urgent safety measures

5.89 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. Procedures relating to urgent safety measures are described in paragraph 9.20-9.23.

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Section 6: Sub-committees

Summary
Sub-committees consist of members of the Research Ethics Committee appointed to carry out functions delegated by the full REC. The decisions of a sub-committee do not need to be ratified by the full committee, unless an issue is specifically referred for further consideration.

Section 6 gives full guidance on the functions of sub-committees. In summary these are:

- Review of new applications for proportionate review
- Considering further information provided by applicants and advice from referees; and confirming the final opinion of the Committee on new applications
- Reviewing amendments and modified amendments
- Monitoring the safety and progress of research with a favourable opinion
- Site-specific assessments for non-NHS sites.

Except for applications under proportionate review, sub-committees should not undertake the primary review of new applications.

The REC can set up a “standing sub-committee” or appoint sub-committees on an ad hoc basis. The Chair should ensure that relevant expertise is available.

A standing sub-committee must consist of at least two committee members, including the Chair or vice-Chair, who can attend meetings or submit written comments regularly. Normally at least four members should be appointed to allow for absences. Special rules apply to proportionate review sub-committees with a mix of members from RECs within the same centre.

For an ad hoc sub-committee the Chair, vice-chair or alternate vice-chair must take part, plus at least one other member of the committee.

Deputy members may take part in place of their lead member but should not be appointed as members of a sub-committee in their own right. One member may be co-opted from another REC at any sub-committee meeting reviewing CTIMP. Other meetings may co-opt two members.

Sub-committee business may be conducted at announced, face-to-face or telephone meetings, or in correspondence between the members. When delegating a decision, the REC may require that the matter is considered at a meeting. Otherwise it is at the discretion of the Chair how the business is conducted.

Procedures relating to the submission of written comments, referees, attendance of investigators and observers are essentially the same as for meetings of the full Committee.

Guidance is given on the responsibilities of the Co-ordinator. These are essentially the same as for meetings of the Committee, except that:
• Papers should normally be distributed no later than 3 days before an announced meeting.

• Minutes of telephone meetings should be taken by the Chair if the Co-ordinator cannot follow the discussion using conference facilities.

• Decisions taken by sub-committee should be reported to the full Committee in the Co-ordinator’s report, or the minutes of an announced meeting may be attached to the report.
Statutory provisions

6.1 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

6.2 The general guidance from NRES Head Office is that the functions set out in paragraph 6.3 should normally be exercised by a sub-committee of the REC.

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

(i) Review of new applications submitted for proportionate review (see Section 8)
(ii) Review of notices of substantial amendment and modified amendments relating to an application to which the REC has given a favourable opinion (see Section 5).
(iii) Monitoring of research studies to which the REC has given a favourable opinion (see Section 9), including:
   - Review of annual progress reports, 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 annual safety reports together with lists of SSARs (in the case of CTIMPs)
   - Review of serious adverse events (in the case of other research)
   - Review of any other safety reports.
(iv) Site-specific assessments for non-NHS sites (see Section 4).

6.4 Sub-committee meetings may undertake a mix of the business listed in paragraph 6.3. 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.)

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

6.6 Sub-committee business may be conducted at face-to-face meetings, by telephone meetings (see paragraphs 6.16-4.1713-6.14) or by correspondence between the members (see paragraphs 6.20-6.22). When delegating a decision to a sub-committee, the REC may require that a face-to-face or telephone meeting is arranged. Otherwise it is at the discretion of the Chair how the sub-committee business is conducted. Consideration should be given to the significance of the matters to be discussed.
Authority of sub-committees

6.7 A sub-committee has delegated authority to take decisions on behalf of the REC on the matters listed in paragraph 6.3 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

6.8 A sub-committee may be established in either or both of the following ways:

(i) **Standing sub-committee.** A standing sub-committee may be established. This should consist of at least three members who would be able to attend meetings or submit written comments on a regular basis. It is suggested that at least four members should normally be appointed to allow for absences. The membership should include at least the Chair and/or vice-Chair or alternate vice-Chair. Other members may be invited to contribute to standing sub-committee business as appropriate. A decision to establish a standing sub-committee should be taken at a full meeting of the REC.

(ii) **Ad hoc sub-committee.** The REC may appoint members of a sub-committee on an entirely *ad hoc* basis, depending on the particular business to be conducted. For example, meetings to consider further information provided by applicants and to confirm the REC’s ethical opinion might be attended by the relevant lead reviewer. The Chair, vice-Chair or alternate vice-Chair should be present at all meetings. Ad hoc sub-committees may be appointed at a full meeting of a REC, or arranged by the Co-ordinator with the agreement of the Chair.

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

6.10 A standing committee established primarily to undertake proportionate review of new applications may consist of a mix of members from the RECs supported by the same REC centre, subject to the following:

- The sub-committee should have an appointed Chair and vice-Chair (who may be from different RECs);
- Meetings of the sub-committee, or business conducted in correspondence, should normally be chaired by the sub-committee Chair or vice-Chair;
- 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").
Any business undertaken by the sub-committee other than proportionate review should relate to the host REC only, and should not include any business relating to CTIMPs.

6.11 Deputy members should not be appointed to serve on sub-committees in their own right, but may attend sub-committee meetings or submit written comments in place of their lead member.

Quorum for meetings

6.12 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 a Committee officer (see also paragraph 6.10) and at least one lay member.

6.13 The quorum for any other sub-committee business 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. The Chair and vice-Chair together constitute a quorum. It is desirable but not essential for a lay member to be involved.

6.14 The Chair is responsible for ensuring that appropriate expertise is available to any sub-committee, depending on the business to be undertaken.

Distribution of papers

6.15 The agenda and papers for sub-committee meetings should normally be distributed no later than 3 days prior to the meeting. The local requirements for distribution of papers should be discussed and agreed by members of the sub-committee.

Telephone meetings

6.16 Sub-committee meetings may be conducted over the telephone. Where available, teleconferencing or video-conferencing facilities should be used. If such facilities are not available, it is acceptable for business involving the Chair and one other member only to be conducted over a normal telephone line.

6.17 Where a telephone meeting is necessary, the Co-ordinator should issue an agenda and papers for the meeting according to normal procedure. Matters on the agenda may be considered in written correspondence or e-mail between the members concerned prior to the telephone meeting, provided that the decisions of the sub-committee are then formally made at the meeting. Minutes of telephone meetings should be prepared by the Co-ordinator. Where he/she is unable to follow the
telephone discussion, the Chair should provide written notes for incorporation in the minutes.

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Submission of written comments prior to meetings

6.18 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. The minutes should record the submission of written comments.

6.19 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.

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Conduct of sub-committee business by correspondence

6.20 Except for appeals reviewed by GTAC under paragraph 7.41, sub-committee business may be conducted by correspondence, including e-mail. The Co-ordinator should list the business in an email to the members concerned with deadlines for receipt of comments. A separate agenda document is not required in this case.

6.21 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. The Co-ordinator should ensure that records are kept of the comments of all members concerned until the minutes have been ratified (see paragraph 14.8).

6.22 Minutes of the business should be prepared by the Co-ordinator. All decisions made in correspondence should be recorded in the Co-ordinator's next report for the REC (see paragraphs 2.15-2.20).

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Proportionate review: lead reviewers and contact with applicant

6.23 The Co-ordinator should appoint a lead reviewer for each application to be reviewed by a proportionate review sub-committee, in consultation with the Chair as necessary.

6.24 Lead reviewers may contact the Chief Investigator 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. The Co-ordinator should notify the Chief Investigator of the name of
the lead reviewer and advise that they may be contacted prior to the meeting.

6.25. 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.

**Attendance of investigators**

6.26 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 or
to be available by phone (or by teleconference or videoconference) where this
would be helpful in providing further clarification, resolving issues of concern to the REC and
reaching an early decision.

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**Co-opted members**

6.27 Under the Clinical Trials Regulations, a REC may only co-opt one additional member
at any sub-committee meeting. Therefore, for any business relating to CTIMPs, only
one co-opted member may participate. For any other business, normally a maximum
of two members may be co-opted. In the case of standing proportionate review sub-
committees, more than two members may participate from RECs other than the host
REC (see paragraph 6.10).

6.28 Except in the case of co-opting to GTAC, a person may be co-opted as a member
only if he/she is or has been a member of a REC (see guidance on indemnity in
paragraph 2.41-2.44).

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**Referees**

6.29 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 2.49(iii) should be followed. It is not expected
that advice from specialist referees should be required by proportionate review sub-
committees. Where material ethical issues are raised requiring specialist advice, the
application should be referred for review at a full committee meeting and the usual
arrangements made to seek advice from referees.

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**Observers**
6.30 The procedures for attendance of observers at REC meetings (see paragraphs 2.65-
2.68) also apply to sub-committee meetings.

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Responsibilities of the Co-ordinator

6.31 The responsibilities of the Co-ordinator or assistant Co-ordinator in relation to sub-
committee meetings are as follows:

(i) Preparing the agenda for meetings
(ii) Distributing the agenda and papers at least 3 days prior to a meeting
(iii) Preparing the venue
(iv) Recording apologies for absence prior to meetings
(v) Recording attendance by members and referees at meetings
(vi) Advising meetings as necessary on compliance with standard operating
procedures
(vii) Making a written record of meetings
(viii) Preparing the minutes of the meeting (incorporating any notes made by the
Chair in the case of telephone meetings).
(ix) Following up the decisions taken as appropriate.

6.32 The responsibilities of the Co-ordinator or Assistant Co-ordinator in relation to sub-
committee business conducted in correspondence are:

(i) Distributing papers to members and specifying dates for written comments to be returned
(ii) Arranging for written comments to be reviewed by the Chair
(iii) Following up the decisions taken as appropriate
(iv) Recording the decisions taken and the members involved in the Co-
ordinator’s Report
(v) Preparing minutes of the business (see paragraph 6.22)
(vi) Destroying written comments from members once the minutes have been ratified (see paragraph 14.8).

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Minutes of sub-committee meetings

6.33 The requirements of paragraphs 2.75-2.77 apply to the minutes of sub-committee
meetings in the same way as for REC meetings.
6.34 Minutes of sub-committee meetings should be ratified by the members or deputy members who were present. This may be done by correspondence or at a subsequent meeting of the sub-committee. Following ratification, the minutes should be signed and dated by the Chair and by the Co-ordinator or assistant Co-ordinator.

6.35 The minutes of sub-committee meetings are confidential, and paragraph 2.83 applies in the same way as for REC meetings.

6.36 The REC should be notified of the decisions taken by sub-committee (see paragraphs 2.15-2.20).
Section 7: Further review of research given an unfavourable opinion

Summary

Three options are available to an applicant who has received an unfavourable opinion:
Section 6 gives full guidance on the functions of sub-committees. In summary these are:

- Submission of a new application
- Appeal
- Request for variation of opinion, if the opinion is based on factual error or misunderstanding (see Section 3)

New applications and appeals are given a new REC reference number in RED.

New applications

The new application should take account of the ethical concerns raised previously. The form must declare that the research proposal has been reviewed before. If SSA is required for non-NHS sites, new SSI forms must be submitted and the SSA process repeated.

A locally allocated application should normally be booked for review with the same REC that reviewed the previous application. For applications allocated through CAS the normal allocation procedure will be followed.

When the application is being reviewed by a “second REC”, the previous documentation should be obtained from the “first REC” and included with the papers for members.

In principle an applicant may continue to submit new applications relating to the same research project. Further evidence of scientific review may be requested before a new application is validated. An applicant may be considered “vexatious” by the NRES Head of Operations in consultation with the Chair and operational managers if a genuine attempt is not being made to address the concerns raised previously.

Appeals

The applicant can appeal against the decision of the “first REC” and seek another opinion of the same application from a “second REC”.

The Clinical Trials Regulations make statutory provision for appeals relating to CTIMPs. The functions of UKECA relating to appeals are undertaken by NRES and the same system of appeal applies to CTIMPs and other research.

Notice of appeal should be sent in writing to the nominated operational manager (“the appeal manager”). The notice must be sent within 90 days of the previous opinion. Appeals will normally be allowed though NRES reserves the right to disallow an appeal.

The application and supporting documentation should not be revised but further representations may be made relating to the opinion given by the first REC.

The appeal manager will appoint a second REC to review the application. Previous documentation should be obtained from the first REC and included with the papers for the
members at the meeting. It is highly desirable that the Chief Investigator should attend the meeting if possible. Any SSAs underway should continue and will be transferred to the second REC for processing site approvals.

If the "second REC" also gives an unfavourable opinion there is no provision for further appeal but a new application may be submitted.

Under the Regulations, special procedures apply to any appeal against an unfavourable opinion by GTAC on a CTIMP for gene therapy.
Options available to the applicant

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

(i) He/she may submit another application, which should be reviewed as a new application (paragraphs 7.2-7.13);

(ii) He/she 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 7.14-7.53).

(iii) Request may be made to vary the opinion where it appears to be based on error or misunderstanding (see paragraphs 3.60-3.64).

Submission of a new application

General procedures for review of new applications

7.2 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 first REC when rejecting the previous application. 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 REC operational manager and the REC’s appointing authority (see paragraphs 9.89-9.91).

7.3 A new application should be entered on RED by the Co-ordinator, and will receive a new REC reference number. The validation procedures in Section 1 apply. In addition to the usual validation criteria, the following requirements apply (see paragraph 1.49):

- A covering letter has been provided, explaining how the new application addresses the reasons given for the unfavourable opinion.
- Any changes to study documents have been highlighted, and documents given revised version numbers and dates where applicable.

7.4 The application should be ethically reviewed according to normal procedures. In the case of studies requiring SSA for non-NHS sites, new applications for SSA should be submitted by Principal Investigators and processed by SSA RECs in the normal way.

7.5 Where the application is being reviewed by a different REC, the Co-ordinator of the second REC should contact the Co-ordinator of the first REC to request a copy of the correspondence relating to the previous review. This should be included with the documentation submitted to members at the meeting.
Booking and submission of new applications

7.6 It is highly desirable that the new application is re-booked with the first 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 he/she prefers, except where the first REC is the only REC with the legal authority to review the application (see paragraph 1.10).

7.7 In the case of applications booked direct with a REC office or via a Local Allocation System, the Booking Co-ordinator should offer the applicant the option of booking with another appropriate REC where there is a significant risk that the first REC might not be able to give an opinion within 60 days, for example due to the following:

- The application is received, or is likely 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 sufficient members.

7.8 Review by a second 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 first REC, the validation date will be the closing date for submissions to the next available meeting.

7.9 Where the new application is booked through CAS, the applicant should be offered the first available meeting slot at an appropriate REC. If the applicant agrees, the application should be assigned to this meeting.

7.10 If the applicant declines the first available slot, the application should normally be allocated back to the first REC. If its next agenda is full, the applicant may opt to wait for the following meeting, or other options may be discussed.

7.11 If the applicant declines the first available agenda slot, the validation date will be the closing date of the meeting of the REC to which the application is assigned.

Vexatious applicants

7.12 An applicant may in principle continue to submit new applications relating to the same research proposal. However, following review of three applications (including any withdrawn applications), 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 his/her 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.

7.13 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 REC operational manager based on the grounds in 7.12.

(ii) The REC operational manager should investigate the application history in consultation with the Chair and Co-ordinator of the REC most recently involved in review of the project and, if appropriate, with other RECs concerned.

(iii) If the REC operational manager considers that the criteria in paragraph 7.12 apply, a recommendation should be made to the NRES Head of Operations to declare the applicant vexatious.

(iv) The Head of Operations will consider the recommendation in consultation with the REC operational manager and the NRES Director. If it is endorsed, notification should be sent to the CAS Co-ordinator and all RECs that no further applications related to the project in question should be accepted for review until further notice. 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 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 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 ethical 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

7.14 Where a recognised REC has given an unfavourable opinion on a CTIMP, the Clinical Trials Regulations allow the Chief Investigator (except where paragraph 7.15 applies) to send a written notice to UKECA stating that he/she wishes to appeal against the opinion and making representations. Such notice must be given within 90 days 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.

7.15 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” (Scotland A REC) under the Adults with Incapacity (Scotland) Act 2000.

7.16 The Regulations make special provision for appeal in the case of any unfavourable opinion given by GTAC on a CTIMP. (Procedures for appeals relating to GTAC applications are set out in paragraphs 7.36-7.50.)

7.17 The policy of the Department of Health and the devolved administrations is that NRES should exercise the functions of UKECA relating to appeals, or AAPEC in the case of appeals against unfavourable opinions given by the AAPEC RECs. The procedures for appeals apply to any research reviewed by a REC in the UK under these SOPs, except where paragraph 7.15 applies.

Appeal procedures

Notice of intention to appeal

7.18 When sending SL6 or SL15 giving 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.

7.19 Notice of intention to appeal should normally be given in writing within 90 days of the date of the letter confirming the unfavourable opinion of the first REC. 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. Appeals will normally be accepted, though NRES reserves the right to disallow an appeal.

7.20 Notice should be given by the applicant in writing to the Appeal Manager, who is the NRES Head of Operations (or if unavailable the Deputy Head of Operations). The Appeal Manager should then make arrangements to allocate the application to another REC for review, taking into account geographical proximity to the Chief Investigator’s professional base and any requirement for review by a flagged REC, and for an agenda slot to be booked at its next meeting (where appropriate, through CAS).

7.21 The Appeal Manager has the discretion to accept a notice of intention to appeal given after 90 days has elapsed, taking account of any exceptional circumstances.

7.22 The Appeal Manager should notify the Chief Investigator in writing whether or not the appeal is allowed. Where the appeal is allowed, SL36 should be sent. The letter should state which REC has been allocated to review the application, the date of the meeting at which it has been booked, the new REC reference number and the closing
date for submission. Copies should be sent to the Co-ordinators of both RECs. Where the appeal is disallowed, the Appeal Manager should send SL36A to the Chief Investigator giving reasons.

7.23 The validation date for the appeal will normally be the date of the letter to the applicant confirming that the appeal is allowed. 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.

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Preparation for the appeal

7.24 The applicant is not permitted to make any revision to the application reviewed by the first REC. It is therefore the responsibility of the Co-ordinator of the first REC to send the application form and all accompanying documentation to the second REC by the specified closing date, together with all correspondence relating to the application.

7.25 If the first REC gave an unfavourable opinion at the Committee 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.

7.26 Once the second REC has accepted the appeal a copy of the application will be received on RED. The application does not need to be re-entered on RED. There is no requirement for the normal validation letter to be sent. The Chief Investigator should be notified of the arrangements for the appeal by the Co-ordinator of the second REC using SL36B.

7.27 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.

7.28 When distributing the application documentation to members prior to the meeting, the Co-ordinator of the second REC should include a copy of the correspondence relating to the application and any representations submitted by the applicant.

7.29 The Co-ordinator of the second REC should invite the Chief Investigator to the meeting. It is particularly important that the Chief Investigator attends the meeting if at all possible so that a full discussion can take place on the main ethical issues.

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Review of applications on appeal

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

7.31 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.

7.32 In the case of studies requiring SSA, the second REC assumes all responsibilities relating to the approval of non-NHS sites, taking account of advice received from site-specific assessors. The SSA process already underway should continue. There is no need for new applications to be submitted. Any SSAs which have been suspended should restart with a new clock.

7.33 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 amendments.

7.34 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 (either SL6 or SL15) 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 7.2), 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.

7.35 The second REC should copy all correspondence on its review to the first REC.

Appeal against unfavourable opinion by GTAC

7.36 This section makes special provision for appeals against unfavourable opinions by GTAC on applications involving:

- A gene therapy CTIMP
- Any other CTIMP
- Stem cell therapy derived from stem cell lines.

7.37 Where GTAC gives an unfavourable opinion on any other type of application, the normal appeals procedures set out in paragraphs 7.14–7.35 apply.

7.38 Where the Chief Investigator wishes to appeal against an unfavourable opinion by GTAC within the scope of paragraph 7.36, he/she may within 14 days of being notified of the opinion either

(a) Send a written notice to GTAC, requiring GTAC to review its opinion; or

(b) Send a written notice of intention to appeal to UKECA, setting out representations with respect to the opinion.
Notice of appeal to GTAC

7.39 Notices to GTAC under paragraph 7.38(a) should be sent to the GTAC Co-ordinator by letter or email, copied to the NRES Head of Operations. If the communication is not copied to the NRES Head of Operations, the GTAC Co-ordinator should notify him/her immediately.

7.40 GTAC has the discretion to accept a notice of appeal after 14 days has elapsed, taking account of any exceptional circumstances.

7.41 Where such a notice is received, the opinion should be reviewed by GTAC in sub-committee, either at a face-to-face meeting or a telephone meeting arranged under paragraphs 6.16-6.17. The sub-committee should comprise the Chair or a vice-chair together with at least two other members. External referees may be co-opted on to the sub-committee at the discretion of the Chair. The CI and/or sponsor’s representative may be invited to attend the sub-committee meeting or to be available by phone.

7.42 The sub-committee should decide whether to confirm GTAC’s unfavourable opinion or to vary the opinion to a favourable opinion. The CI should be notified of the decision in writing within 60 days of receipt of the notice of appeal.

7.43 Where GTAC upholds its unfavourable opinion under paragraph 7.42, the CI may submit a further notice of intention to appeal to UKECA within 14 days under paragraph 7.44.

Notice of intention of appeal to UKECA

7.44 The CI may give notice of intention to appeal to UKECA either:

(a) within 14 days of being notified of an initial unfavourable opinion by GTAC, or

(b) within 14 days of being notified by GTAC that it has confirmed the unfavourable opinion following appeal under paragraph 7.42.

7.45 The functions of UKECA relating to appeals against unfavourable opinions by GTAC have been delegated to NRES. The CI should send any notice of intention to appeal against an unfavourable opinion by GTAC to the NRES Head of Operations, who will act as the Appeal Manager. The notice may include representations with respect to the opinion of GTAC. The applicant may not make changes to the application or supporting documentation. Appeals will normally be accepted, though NRES reserves the right to disallow an appeal.

7.46 The Appeal Manager has the discretion to accept a notice of intention to appeal given after 14 days has elapsed, taking account of any exceptional circumstances.

7.47 The Appeal Manager should notify the Chief Investigator in writing whether or not the appeal is allowed. Where the appeal is allowed, the CI should be informed of the arrangements for reviewing the application on appeal.

7.48 The Appeal Manager should establish an appeal panel as soon as possible to reconsider the opinion together with any representations set out by the CI. The panel must be comprised of a chair together with at least 6 other panel members. The chair and panel members may include:
• officers or members of GTAC
• officers or members of other RECs
• any other person with relevant expertise.

The panel must include at least one lay person, who may be either a current or former lay member of a REC or any person meeting the criteria for appointment as a lay member. In determining the appropriate composition of the panel, the Appeal Manager will take into account the reasons for the unfavourable opinion, the representations made by the applicant and the appropriate balance of expertise required to undertake a further review. The advice of the Chair of GTAC will be taken into account. A majority of the panel should be individuals not currently serving as members of GTAC.

7.49 The GTAC Co-ordinator will act as secretary to the appeal panel. A meeting of the panel should be arranged as soon as possible once the membership of the panel has been determined. The Chief Investigator and sponsor’s representative should be invited to attend.

7.50 The applicant is not permitted to make any revision to the application reviewed by GTAC. The GTAC Co-ordinator should arrange for the original application and supporting documentation, together with the correspondence on the initial review (and any correspondence on a previous appeal to GTAC under paragraphs 7.39-7.43) and any representations sent to the Appeal Manager to be sent to members of the appeal panel at least 14 days before the panel meeting.

7.51 The application should be reviewed by the appeal panel in accordance with the standard procedures for review of any new application by a REC. The aim is for a final decision to be notified to the CI within 30 days of receipt of the notice of intention to appeal by the Appeal Manager, not including any time taken by the applicant to respond to one written request from the panel for further information or clarification, but the Appeal Manager may allow an extended period if required.

7.52 If the appeal panel upholds the unfavourable opinion, no further appeal is permitted on this application. The CI may however submit a new application to GTAC, suitably revised to take account of the ethical concerns raised in the opinion.

7.53 If the appeal panel gives a favourable opinion of the application following further review, the trial is considered to have a favourable opinion under the Clinical Trials Regulations. GTAC remains the main REC for purposes of reviewing substantial amendments and all other matters relating to monitoring of the trial under Section 9 of the SOPs.
Section 8: Expedited and proportionate review

General policy

8.1 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 days (depending on the type of trial), which may be suspended once pending receipt of further information from the applicant (see paragraphs 3.1-3.2).

8.2 However, the policy of the UK Health Departments in GAfREC recognises that some research may be suitable for expedited review, for example:

- Research undertaken in a public health emergency
- Research raising no significant issues of research ethics, including projects involving straightforward issues which can be easily identified and managed by the research team in accordance with published guidelines on ethics and good research practice

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

Research undertaken in a public health emergency

8.4 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 a CTIMP or other health-related research study to commence as quickly as possible.

8.5 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

8.6 Where a research sponsor or Chief Investigator believes that such circumstances may apply, he/she should contact the NRES Head of Operations and/or the REC operational manager in Scotland, Wales or Northern Ireland (as applicable) directly for advice. The Co-ordinators or Chairs of individual RECs have no authority to expedite or set aside the normal procedures for ethical review in such cases.

8.7 For studies taking in place in England, including those with sites in another UK country, the NRES Head of Operations will consider the request against the criteria in paragraph 8.5 and in consultation with the NRES Director and 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.

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

8.9 The NRES Head of Operations 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 Head of Operations 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 NRES specifically for the review of this application. If the application relates to a clinical trial of an investigational medicinal product, the REC will need to be legally recognised by UKECA. The membership of the REC will be a matter for the discretion of the Head of Operations but should include both lay members and relevant experts. A Chair and Co-ordinator should be appointed by the Head of Operations.

8.10 The Head of 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 Head of Operations may specify the time periods within which each stage of the process should be completed.

8.11 Where the application requires site-specific assessment of non-NHS sites, the normal procedures for SSA may be waived at the discretion of the Head of Operations. The sponsor or Chief Investigator should provide the appointed REC with appropriate evidence of the adequacy of local sites, investigators and facilities. The Chair of the appointed REC may require that the SSI form is completed for each proposed non-NHS site and submitted direct to the appointed REC for assessment together with the CV for each Principal Investigator. The Chair or Co-ordinator of the appointed REC may consult relevant RECs or other organisations for advice by telephone, e-mail or fax.

8.12 Where a favourable ethical opinion is given by a specially appointed REC under paragraph 8.6(ii), and that REC is later abolished, the NRES Head of Operations
should re-assign the responsibilities for monitoring the research and reviewing amendments to another REC.

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Proportionate Review Service

8.13 The Proportionate Review Service (PRS) provides for expedited, proportionate review of research studies raising no significant ethical issues, including projects involving straightforward issues which can be identified and managed routinely in accordance with standard research practice and existing guidelines. Under PRS, new applications are reviewed by a sub-committee rather than at a full meeting of a REC, with the aim of notifying the final decision to the applicant within 14 calendar days of receipt of a valid application.

8.14 Adoption of PRS, and the timing of implementation, is at the discretion of REC operational managers 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. Where PRS is in operation, the procedures set out in these SOPs apply.

8.15 Criteria for determining whether a study is suitable for review through the PRS are developed by NRES in consultation with the National Research Ethics Advisers’ Panel and published on the NRES website and in IRAS. 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.

8.16 Specific procedures applying to the submission and review of applications through the PRS are set out as follows:

- Booking, submission and validation of applications (1.33, 1.35, 1.58-1.63) (Note: Until electronic submission is introduced, PRS applications must be received by the REC within 2 days of booking.)
- Decisions on applications (3.8, 3.12-3.13, 3.16, 3.37, 3.46, 3.52-3.54)
- Sub-committee procedures (6.3-6.5, 6.10, 6.12, 6.23-6.25).

Except where specific procedures are indicated, the SOPs apply to applications reviewed through PRS in the same way as any other application.
Section 9: Monitoring of research given a favourable opinion

Summary

The main REC is not required to monitor the conduct of the research proactively but should keep the ethical opinion under review in the light of progress and safety reports submitted by the sponsor or Chief Investigator, and any other developments in the study. Primary responsibility for monitoring lies with sponsors and employing organisations.

Research should normally start within 12 months of the final opinion letter. If no participant has been recruited within 12/24 months the Chief Investigator should give an explanation of the delay in the annual progress report. If the research does not start within 24 months the REC may review its opinion.

Progress reports on all studies should be sent to the main REC annually by the Chief Investigator using the NRES form. More frequent progress reports may be requested. Progress reports should be reviewed by the Chair or by another member. The Co-ordinator will issue a reminder letter if an annual report is not received.

Safety reporting for CTIMPs is subject to guidance from the European Commission. Sponsors are required to send the main REC expedited reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in the UK and an annual safety report (ASR). The ASR should follow the ICH E2F guideline for the Development Safety Update Report (DSUR) and include a global line listing.

When submitting safety reports, sponsors should complete the covering form issued by NRES. Reports should only be sent to the main REC.

The main REC is not required to review expedited reports of SUSARs. The Executive Summary of the DSUR should be reviewed at least by the Chair and an expert member. Primary responsibility for safety lies with the sponsor. The MHRA has the main regulatory responsibility and will keep the main REC informed about any safety issues.

For other research, Serious Adverse Events (SAEs) that are research-related and unexpected should be notified within 15 days using a separate form issued by NRES.

The Chief Investigator may permit a minor “deviation” from the protocol without notifying the main REC. If the deviation meets the criteria for a “substantial amendment” then it requires ethical review. A serious breach of the protocol or GCP resulting from error or misconduct must be reported.

The main REC should be notified of the conclusion of the study within 90 days, or within 15 days if it has terminated early. For CTIMPs the sponsor should submit the European Commission form. For other research the Chief Investigator should submit the NRES form.

The main REC may review the ethical opinion at any time. Detailed procedures are set out on procedures for considering a possible suspension or termination of the favourable opinion for a non-CTIMP. The sponsor should normally be given the opportunity to address issues of concern before such action is taken, and has the right to appeal.
For guidance on addressing concerns emerging during conduct of a CTIMP, refer to Section 13.

A summary of the final report on the research should be sent to the main REC within 12 months of its conclusion.

Any information relating to possible misconduct or criminal offences relating to research should be passed confidentially by the REC to the REC operational manager and its appointing authority. The REC should not undertake its own investigations.

Statutory requirements

9.1 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 main 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 amendments (see Section 5). 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.

General policy on monitoring of research

9.2 The general policy from NRES is that the main REC should keep under review the favourable ethical opinion given to any research study in the light of regular progress reports and significant developments in the research. This applies equally to CTIMPs and to other types of research, except in relation to safety reporting where different provisions apply.

9.3 Where a study received ethical approval from more than one REC under the system in operation prior to 1 March 2004, the sponsor or Chief Investigator should contact the NRES Head of Operations to request that a single main REC is appointed to take responsibility for monitoring of the research (see paragraph 10.9).

9.4 Other than by means of the reports that the sponsor and investigators are required to submit, the main REC has no responsibility for proactive monitoring of research studies. The accountability for this lies with the sponsor and the employing organisation. Similarly, SSA RECs have no responsibility for proactive monitoring of the local conduct of the research at non-NHS sites requiring SSA.

9.5 The Chief Investigator and representatives of the sponsor may be requested to attend a meeting of the main REC or sub-committee at any time to discuss any ethical or
safety concerns about the research. Similarly, local Principal Investigators may be requested to attend a meeting of the SSA REC or its sub-committee to discuss any new concerns relating to the suitability of the site.

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Commencement of the research

9.6 Research should normally commence within 12 months of the date on which a favourable ethical 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. The commencement date should be stated in the first annual progress report for the research.

9.7 Should the study not commence within 12 months, the Chief Investigator should give the main REC a written explanation for the delay in the first annual progress report (see paragraph 9.11).

9.8 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 9.87-9.102.

9.9 If a study is abandoned prior to commencement, the Chief Investigator or sponsor should notify the main 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 9.82-9.83). If a study is abandoned and it is later proposed to start it afresh, a new application should be made.

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Duration of a favourable ethical opinion

9.10 The favourable ethical opinion of the main 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 paragraphs 9.86-9.93). Extension of the study period is not in itself a substantial amendment, except where it is related to other amendments 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, there is no need to notify or seek approval from the main REC. However, annual progress reports should continue to be submitted if the study duration is extended in this way, giving reasons for the extra time needed to complete the research – see paragraphs 9.12-9.20.)

9.11 It should be noted that continuation of the ethical opinion only applies to the study as described in the application, the protocol and any amendments made by the sponsor. Further applications should be made for ethical approval where required to undertake additional studies. In the case of studies involving human tissue which is “relevant material” under the Human Tissue Act 2004, authority to store the material in England, Wales or Northern Ireland under the terms of this ethical approval expires once the original study has ended (see paragraphs 11.17-11.18).
Progress reports

9.12 Progress reports on all research with a favourable opinion should be submitted to the main REC at least annually. The due date for receipt of the report is 30 days following the anniversary of the date on which the favourable opinion was given. Reports should continue to be submitted at least annually until the end of the study is notified, except where paragraph 9.19 applies. The main REC may request that more regular reports should be submitted, or may request an additional progress report at any time.

9.13 Progress reports should be in the format prescribed by NRES and published on the website. Reports may be submitted by the sponsor or the Chief Investigator, but should always be signed by the Chief Investigator.

9.14 Progress reports should be acknowledged by the Co-ordinator (SL37 may be used) and reviewed at least by the Chair or, at the Chair’s discretion, by one or more members of the Committee (for example, the lead reviewer for the study) or a Scientific Officer. The Committee should be notified of the receipt of the report (see paragraph 2.15). Copies or summaries may be distributed to members.

9.15 It is not necessary for the main REC to re-confirm the favourable ethical opinion for the study each time a progress report is received. The presumption is that the opinion remains valid for the duration of the study, unless the REC has grounds for review.

9.16 Where the Chair or another member, or a Scientific Officer, considers that the progress report gives grounds for reconsidering the REC’s opinion on the research, the matter should be considered at a meeting of the Committee or sub-committee.

9.17 Where a progress report is not received by the due date, the REC Co-ordinator should send the reminder SL38. If the report is still not received after a further period of one month, the Chair should consider what further action should be taken. Further guidance on review of a favourable opinion, including possible suspension or termination, is at paragraphs 9.87-9.102.

9.18 There is no requirement for progress reports to be sent to SSA RECs.

9.19 Following receipt of the first progress report, the Chair of the main REC has the discretion to waive the requirement for further reports on receipt of a written request from the Chief Investigator. This might be appropriate where a study has completed recruitment and intervention, but has a long period of follow-up with minimal involvement of participants.

Urgent safety measures
9.20 The Clinical Trials Regulations provide that the sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect the subjects of a CTIMP against any immediate hazard to their health or safety. The main REC and the MHRA must be notified immediately and in any event within 3 days that such measures have been taken and the reasons why. The policy from NRES is that these requirements should apply to all other research with a favourable opinion from a REC.

9.21 The initial notification to the REC should be by telephone. Notice in writing should be sent within 3 days. The notice should set out the reasons for the urgent safety measures and the plan for further action.

9.22 The REC is not required to approve urgent safety measures. However, notifications of urgent safety measures should be reviewed at a meeting of the main 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 amendments 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.

9.23 Where urgent safety measures are taken by a Principal Investigator, the main REC should ensure that the relevant NHS R&D office or SSA REC is informed and should seek its advice if any concern arises about the continued suitability of the site.

Safety reporting in clinical trials of investigational medicinal products

European Commission guidance

9.24 Under the EU Directive the European Commission has issued “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use” (CT3). The guidance describes the requirements for safety reporting by the investigator to the sponsor, and by the sponsor to the Eudravigilance Clinical Trial Module (EVCTM) of EudraCT and to the competent authority and the ethics committee in each member state. CT3 is the main source of guidance for sponsors of CTIMPs in the UK. The following paragraphs summarise the key requirements as they apply to reporting to ethics committees.
9.25 Suspected Unexpected Serious Adverse Reactions (SUSARs), which are associated with the use of an investigational medicinal product (IMP) in the trial, must be notified both to the MHRA and to the main REC in accordance with the requirements of the Directive for expedited reporting. This includes SUSARs associated with an active comparator drug used in the trial. **In the case of the main REC, the sponsor is only required to report in expedited fashion SUSARs occurring in the concerned trial in the UK.** SUSARs occurring in the trial outside the UK are subject to expedited reporting to all relevant competent authorities, but do not need to be notified in this way to ethics committees in the UK. They should however be included in line listings submitted with annual safety reports once the trial has started in the UK (see paragraphs 9.37-9.44). Where RECs receive expedited reports of non-UK SUSARs, the Co-ordinator may arrange for them to be shredded and there is no requirement to acknowledge receipt.

9.26 There is no requirement to include reports of non-UK SUSARs, or of SUSARs occurring in other UK trials of the IMP, with the documentation submitted to a REC as part of a new trial application in the UK. 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.

9.27 A serious adverse reaction is an untoward and unintended response to an IMP at any dose, 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, or
(e) consists of a congenital anomaly or birth defect.

The judgement as to whether a reaction is ‘serious’ and the assessment of causality are usually made by the investigator. The investigator’s assessment may not be downgraded by the sponsor. If the sponsor disagrees with the investigator’s causality assessment, both the opinion of the sponsor and the investigator should be provided with the report.

9.28 An adverse reaction is considered to be ‘unexpected’ if its nature and severity are not consistent with the reference safety information (RSI) for the IMP. The RSI is set out in either the Summary of Product Characteristics (SmPC), in the case of a product with a marketing authorisation, or the Investigator’s Brochure for the trial as applicable. The assessment of expectedness is usually made by the sponsor in the light of the RSI.

9.29 A SUSAR which is **fatal or life-threatening** must be reported to the MHRA and the main REC as soon as possible and in any event within 7 days after the sponsor became aware of the event. If the initial report is incomplete, a complete report must
be submitted within 8 days of sending the first report. If significant new information is received by the sponsor on a case already reported, the clock starts again and this should be provided as a follow-up report within 15 days of receipt of the information.

9.30 A SUSAR which is not fatal or life-threatening must be reported to the MHRA and the main REC as soon as possible and in any event within 15 days after the sponsor first became aware of the event. If an event is initially reported as not fatal or life-threatening and it turns out to be fatal or life-threatening, a follow-up report should be made as soon as possible and within 7 days of the severity of the event becoming known.

9.31 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.

9.32 There is no requirement to provide reports to RECs other than the main REC. Sponsors should not send reports to other RECs. Where they do so, the Coordinator may arrange for the reports to be shredded and there is no requirement to acknowledge receipt.

Format of SUSAR reports

9.33 Reports of SUSARs should be in the format set out in the current version of ICH Topic E2B – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Study Reports, available at http://ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. One SUSAR only should be included in each report. The minimum information required is set out in CT3. A causality assessment should be included in all reports, including assessments from both sponsor and investigator if there is no agreement.

Other expedited safety reports

9.34 The European Commission guidance notes that other 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 subjects, 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 subject 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 subjects.

9.35 These events/observations are not to be reported as SUSARs but might require other action such as urgent safety measures, substantial amendments or early termination of a trial. Where such actions are not taken the Commission guidance recommends 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.

Unblinding of SUSAR reports

9.36 In the case of double-blinded trials, the European Commission guidance recommends that the sponsor should normally report SUSARs unblinded to competent authorities, ethics committees and EVCTM. (Any waivers of the requirement for unblinded reporting should be agreed with the MHRA.) Unblinded information should only be accessible to those who need to be involved in safety reporting or who are involved in ongoing safety evaluation during the trial. The blind should be maintained for persons responsible for the ongoing conduct of the study (e.g. study management, monitors, investigators) or for analysis and interpretation of results. Investigators should only receive unblinded information if necessary for safety reasons.

Annual safety reports

9.37 For each IMP being tested in the trial, the sponsor should provide the main REC with an annual report on the safety of subjects in all clinical trials of the product for which the sponsor is responsible, whether in the UK or elsewhere.

9.38 All annual safety reports should be in the format for Development Safety Update Reports (DSUR) set out in the ICH E2F guideline (available at http://ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html). This guideline, which was adopted by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) in September 2010 and comes into effect
on 1 September 2011, establishes a common standard for periodic reporting on drugs under development among the ICH regions. It meets the standards required for annual safety reports on CTIMPs undertaken in the EU.

9.39 The main objective of the ASR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to an investigational drug, whether or not it is marketed, by:

(i) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the safety of the IMP (as defined by the Reference Safety Information in place at the beginning of the period, i.e. by the Investigator Brochure or SmPC as appropriate);

(ii) describing new safety issues that could have an impact on the protection of trial subjects;

(iii) summarising the current understanding and management of identified and potential risks; and

(iv) providing an update on the status of the clinical investigation/development programme and study results.

ASRs should concentrate primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects.

9.40 The ASR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period, including therapeutic use of an investigational drug (e.g. expanded access or compassionate use programmes). In addition, it should include any other significant findings relevant to the safety of the IMP (e.g. from observational, epidemiological or non-clinical studies).

9.41 The recommended format and content of the ASR (as set out in the ICH E2F guideline) is summarised at Annex E. It should include an Executive Summary which provides a concise summary of the important information in the report and is suitable for review by REC members as a stand-alone document.

9.42 ASRs should include or be accompanied by a line listing of all Suspected Serious Adverse Reactions (SSARs) occurring in relevant trials during the year, including both expected and unexpected reactions. Line listings should include SSARs occurring in other EU member states or worldwide, as well as those in the UK. SSARs related to active comparators or placebo used in relevant trials should be included. (There is no need for a separate ASR for comparators.)

9.43 If a sponsor is conducting several CTIMPs in the UK with the same IMP, one safety report may be prepared covering all relevant trials. The report should be sent to each main REC concerned. A separate cover sheet should normally be submitted for each trial (see paragraph 9.53).

9.44 ASRs reports should be sent to the main REC as soon as practicable after the end of the reporting period, and within 60 days at the latest. It is not necessary to send copies of ASRs to other RECs.
Reporting timeframe for ASRs

9.45 The reporting timeframe for ASRs starts with the date of the first authorisation of the trial by a competent authority in any Member State of the European Economic Area. It is not defined in relation to the date on which the main REC gave a favourable opinion for the trial.

9.46 For UK-only clinical trials that commenced before 1 May 2004, the reporting period starts with the issue date of the CTX letter or first DDX exemption letter by the MHRA (or previously by the Medicines Control Agency).

9.47 Where the report covers more than one clinical trial, the reporting period starts on the date on which the first of these trials was authorised in any Member State.

9.48 If the sponsor is the marketing authorisation holder of the tested IMP, the reporting period starts with the International Birth Date (IBD). If the IMP is granted a marketing authorisation for the first time in any Member State while it is being tested in a clinical trial, the reporting period would change from the first date of authorisation to the IBD.

9.49 The statutory requirement to provide ASRs starts when the first participant is recruited at a UK trial site. (For guidance on notifying significant safety information prior to the start of the trial, see paragraph 9.26). 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).

9.50 There is no requirement to submit a final safety report with the end of trial declaration.

9.51 Following termination of the trial, any unexpected safety issue that changes the risk/benefit analysis and is likely to have an impact on the subjects who have participated in it should be reported as soon as possible to the MHRA and the main REC together with proposed actions.

Submission of safety reports

9.52 Expedited and annual safety reports will normally be submitted by the sponsor, but may also be submitted by the sponsor’s legal representative or the Chief Investigator for the study. Reports should normally be sent by email. Extensive line listings may be submitted on CD at the discretion of the REC office (three copies of the CD should be provided).

9.53 Each submission to the main REC should be accompanied by the Safety Report form for CTIMPs, which is a standard cover sheet published on the NRES website. A single form may be used for the submission of several safety reports relating to the
same trial. The form should specify the trial concerned and enclosures should be individually listed and referenced. Reports should not normally cover more than one trial. However, the REC may permit this where two trials are very closely connected, for example a main study and an extension study with the same treatment regime.

9.54 The Co-ordinator should acknowledge receipt of all written reports within 30 days by signing and returning a copy of the form to the person making the submission. The form should not be copied to investigators in the case of double-blind trials as this may compromise the blind.

Responsibilities for monitoring the safety of clinical trials

9.55 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 by the Commission guidance to establish an independent Data Monitoring Committee (DMC) to advise on safety issues. (Guidance for RECs on DMCs is available on the NRES website.) The sponsor has a duty to take action, which may include urgent safety measures, protocol amendments or even the suspension or termination of a trial, where the safety profile or the risk/benefit analysis changes significantly.

9.56 Sponsors are required to submit complete data on all SUSARs occurring in EU member states to EVCTM. This enables the relevant competent authorities, in collaboration where necessary, to maintain an effective overview of the safety issues in a clinical trial. In the UK regulatory context, the MHRA will actively monitor the safety of clinical trials through its access to the European databases. Where the MHRA raises safety concerns with the sponsor, it will directly inform the main REC so that any implications for the ethics of the trial can be considered in parallel.

9.57 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.

9.58 The main REC should therefore review safety reports in accordance with the following guidance.
9.59 Expedited reports of SUSARs or other occurrences should be acknowledged and filed by the Co-ordinator. They do not need to be seen by the Chair. There is no requirement for the Committee to be notified routinely of the receipt of expedited reports, or for any review to be carried out, as the overall safety of the trial cannot be assessed on the basis of such limited data. Reference may subsequently be made to reports of SUSARs where an expert member or referee considers that this may be useful in the context of safety reports about the trial as a whole.

9.60 Annual safety reports should be reviewed at least by the Chair and, unless the Chair has appropriate expertise, by an expert member or referee. The latter should normally be a clinical pharmacologist, a trial pharmacist or a specialist in the disease field. The review may take place in correspondence or at a sub-committee or Committee meeting. The review may be confined to the Executive Summary. The REC is not required to make a detailed assessment of the report as a whole or the line listings. The purpose of the review is to:

- Check the accuracy of the risk/benefit analysis as described in the participant information sheet
- Consider the possible need for new information to be given to participants and their consent sought to continue in the study
- Consider any other issue that may be relevant to the ethics of the trial.

9.61 Where concerns arise about any of the above, the REC 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 3.82). The Chief Investigator may be requested to attend a meeting of the sub-committee or Committee to discuss the concerns of the REC.

9.62 Where findings and recommendations from DMCs are received by the main REC (see paragraph 9.34(c)), they should be reviewed in the same way as ASRs.

9.63 The Committee should be notified in the Co-ordinator’s report (see paragraph 2.15) of the receipt of ASRs and recommendations from DMCs. The report should state who has reviewed the report, and summarise any concerns that have arisen and the further action taken. Where appropriate, the concerns may be discussed at a meeting of the Committee.

Communications with MHRA on safety issues

9.64 The main REC should draw the attention of the MHRA to any substantial concerns about the safety of trial subjects, the accuracy of the risk/benefit analysis or the need for new information to be given to subjects. Communications should be sent to the Head of the Clinical Trials Unit by email (see paragraph 13.9). SL16 may be used. The correspondence will be acknowledged.
9.65 Where the MHRA has concerns about the safety of trial subjects or there is a change in the risk/benefit analysis, it will keep the main REC informed of any action it takes. The Head of CTU will ensure that any relevant correspondence with the sponsor is copied to the main REC. The main REC may seek further information or clarification from the Head of CTU by email or telephone. It may also recommend that the CTU takes action in relation to the CTA, for example to request amendment of the participant information sheet.

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Safety reporting for other research

9.66 In research other than CTIMPs, a Serious Adverse Event (SAE) is defined as 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; or
(f) is otherwise considered medically significant by the investigator.

9.67 An SAE occurring to a research participant should be reported to the main 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.

9.68 Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the NRES website.

9.69 The Chief Investigator should include a report on the safety of participants in the annual progress report.

9.70 Individual reports of SAEs should be reviewed at a sub-committee or Committee meeting.

9.71 There is no requirement to provide reports to RECs other than the main REC.

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Protocol deviations
9.72 A protocol deviation is a planned departure from the requirements of a study protocol to deal with unforeseen circumstances. Such deviations should be agreed with the sponsor and Chief Investigator in advance or, in the case of an urgent safety measure, as soon as possible after the event. Minor protocol deviations may be considered minor (or “non-substantial”) amendments and do not need to be routinely notified to the main REC. However, if the deviation would meet the criteria for a “substantial amendment” it should be notified to the main REC and an ethical opinion sought. In particular, where the deviation is made to protect a subject from an immediate hazard to their health or safety, this should be notified to the main REC as an urgent safety measure and reviewed accordingly (paragraphs 9.20-9.23).

9.73 Where the deviation is necessary due to errors or inadequacies in the protocol, the sponsor is responsible for making appropriate amendments. If the amendments are substantial, they should be submitted to the main REC for ethical review before they are implemented (see Section 5). There is no provision in the Regulations for ethics committees to give an opinion on proposed deviations relating to individual participants (for example, to waive the eligibility criteria for a particular participant). RECs should not review such proposals except where the sponsor notifies a substantial amendment relating to the general conduct of the trial.

Protocol violations

9.74 A distinction should be made between “protocol deviations”, which are agreed with the sponsor and Chief Investigator either in advance or as soon as possible after the event, and “protocol violations”, which are made without permission as a result of error or fraud/misconduct.

9.75 The primary responsibility for investigating protocol violations and taking corrective action lies with the sponsor. It is not necessary to notify the REC of minor protocol violations unless they constitute a “serious breach” (see paragraphs 9.107-9.118). Where a sponsor voluntarily notifies the REC of a minor protocol violation, the Coordinator should acknowledge receipt and send the report to the Chair for information. There is no need for any further action unless the Chair considers that the violation, taken alone or in combination with other reports of minor violations, should be treated as a serious breach.

Temporary halt of the research

9.76 When the sponsor halts a CTIMP temporarily (whether it is a halt of the whole trial or at individual trial site(s)), the MHRA and main REC should be notified within 15 days by submission of the Notification of Substantial Amendment form prescribed by the European Commission (see paragraph 5.4). The form 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 amendment should be reviewed by the main REC in the normal way.

9.77 To restart the trial, the sponsor should submit a further Notification of Substantial Amendment form requesting authorisation and a favourable ethical 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 9.79).

9.78 The policy from NRES is that the same procedures should apply to the temporary halt of any other research in order to protect participants from harm. In the case of non-CTIMPs, the NRES Notice of Substantial Amendment form will be used (see paragraph 5.13).

Declaration of the conclusion or early termination of the research

9.79 The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the main REC in writing that a CTIMP has ended within 90 days of the conclusion of the trial. In the case of an international trial, guidance from the European Commission is that 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 all Member States, this may be notified voluntarily (the form for declaring the end of the trial should not be used in this case).

9.80 If the trial is terminated early, the sponsor should notify the main REC within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.81 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 amendment. 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. 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.

9.82 Declarations of the conclusion or early termination of a CTIMP should be in the form prescribed by the European Commission at Annex C to the “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” (ENTR/CT1). A Notice of Substantial Amendment could be submitted alongside a declaration of early termination where it is necessary to seek ethical review of related actions such as informing participants and arranging continuing care and follow-up outside the trial.

9.83 The policy from NRES is that the requirement to notify the main 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 NRES and published on the website.
9.84 All notifications of the conclusion or early termination of a study should be acknowledged by the Co-ordinator (SL39 may be used) and reviewed by the Chair or, at the Chair’s discretion, by another member of the Committee or a Scientific Officer. The Committee should be notified in the Co-ordinator’s 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.

9.85 Once the end of the study has been declared, the REC it is no longer possible to submit notices of substantial amendment.

9.86 Guidance on submission of final safety reports and notification of safety issues following the end of the trial is set out in paragraphs 9.46-9.47.

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Review of a favourable ethical opinion

9.87 The main REC may review its favourable ethical opinion of a study at any time in the light of safety reports, progress reports or any other information received about the conduct of the study. This may include concerns raised by patients, service users, carers or patient organisations, or issues raised by media reports. The Chief Investigator or sponsor may ask the main REC to review its opinion, or seek advice from the REC on any ethical issue relating to the study.

Suspension or termination of opinion on a non-CTIMP

9.88 A favourable ethical opinion on a non-CTIMP may be suspended or terminated by the main 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 site or facilities

(f) Suspension or termination of regulatory approval for the study.

9.89 In the case of multi-site studies, the favourable ethical opinion for a particular site may be suspended or terminated by the main REC following new information received from the site-specific assessor or another source about the suitability of the site. The favourable opinion could continue to apply to other trial sites in these circumstances.

9.90 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) (SL42). 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.

9.91 Immediate termination of the opinion without prior notice or suspension is permitted only where regulatory approval for a study has also been terminated.

9.92 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.

9.93 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.

9.94 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 committee.

9.95 The REC operational manager should be informed prior to issuing a NISTFO or a letter of suspension or termination.

9.96 A decision to terminate an opinion should always be taken at a quorate meeting of the full committee.

9.97 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.

9.98 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 (see paragraph 9.101)
- 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 (see paragraph 9.100)
- any conditions which are to be satisfied before the favourable opinion may be re-confirmed, either generally or at a particular site.

9.99 A copy of the letter should be sent to the Chief Investigator and, in the case of studies including NHS sites, the lead R&D office. In the case of a multi-site study, it is the
responsibility of the sponsor to ensure that other investigators, local collaborators and care organisations are informed. Where the opinion is suspended or terminated at a particular non-NHS site, a copy of the letter should be sent to the Chair of the SSA REC.

9.100 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 is still awaited.

9.101 A sponsor may appeal against a decision to suspend or terminate an opinion. Notice of intention to appeal should be submitted to the REC operational manager in writing within 90 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

9.102 Procedures for review of opinion on CTIMPs are set out in paragraphs 13.28-13.30.

Further reporting after the conclusion of the trial

9.103 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 main 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

9.104 A summary of the final report on the research should be submitted to the main REC 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.) This applies to both CTIMPs and all other research. There is no standard format for final reports. As a
minimum, the main REC should receive information on whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research including any feedback to participants.

9.105 All such reports should be acknowledged by the Co-ordinator (SL40 may be used) and reviewed by the Chair or, at the Chair’s discretion, by another member of the Committee or a Scientific Officer. The Committee should be notified of the receipt of the report in the Co-ordinator’s report. At the discretion of the Chair, copies or summaries may be distributed to members. No further action is required unless the Chair considers that issues are raised requiring discussion at a meeting of the REC or sub-committee.

9.106 If the final report is not received within one year of the conclusion of the research, the Co-ordinator should send a reminder letter (SL41 may be used).

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Serious breaches of the protocol or GCP

Reports by the sponsor

9.107 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 subjects, or the scientific value of the research.

9.108 The sponsor should notify the main REC and relevant regulatory bodies of a serious breach in any study within 7 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.

9.109 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 main REC.

9.110 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 main REC informed what further action the sponsor plans to take. Any such report should be considered at a meeting of the Committee or by a sub-committee. In circumstances where consideration by the main REC is no longer appropriate, for example where the study has closed, any reports provided may be referred to the Health Research Authority for consideration. Where consideration is given by the main REC to reviewing the opinion, either for the whole of the UK or at an individual site, the REC should follow the guidance in paragraphs 9.86-9.93. The matter should be reported to the REC operational manager in line with the guidance in paragraphs 9.98-9.100 and 9.107.
Other reports of possible serious breaches

9.111 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 ethical review or the conduct of research, the Chair or Co-ordinator should pass the information confidentially to the REC operational manager in writing. If the REC concerned is not the main REC for the study, a copy should also be sent to the main REC and its REC operational manager.

9.112 In some cases, information may initially be received directly by REC operational management or by other staff within NRES (including through the NRES Queries Line). Such information will be passed to the relevant REC operational manager.

9.113 The REC operational manager should notify the NRES Head of Operations of all reports received.

9.114 It will be for the REC operational manager, in consultation with senior operational management at NRES, 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 13.21-13.27)*
- MHRA (Devices) *(clinical investigations of medical devices only – see paragraph 13.45)*
- Other regulatory bodies where applicable.

The NRES Head of Operations 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 NRES Head of Operations to bring the matter to the attention of the HRA. The HRA, as the Appointing Authority for NRES RECs, may write to any of the bodies listed above to request further information in relation to the matter.

9.115 It is for the main REC to consider whether any action needs to be taken in relation to the ethical opinion for the research, in particular where there could be an immediate risk to the safety of participants. The main REC may review the favourable ethical opinion for the study or for a particular site (see paragraphs 9.87-9.102). 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.

9.116 A member of a REC who becomes aware of a possible serious breach should report this to the Chair and Co-ordinator of the REC, who will be responsible for reporting the matter in accordance with paragraph 9.114.98.
9.117 Receipt of information under this section includes any report from a member of an investigator’s team of alleged fraud or misconduct.

9.118 Further operational management guidance about reporting and follow-up of possible serious breaches is issued by the NRES Head of Operations.

**Criminal offences**

9.119 The Clinical Trials Regulations create a variety of criminal offences relating to contravention of its provisions. In particular, it is an offence to commence or conduct a CTIMP unless the trial has received both a favourable ethical opinion from a recognised REC and a Clinical Trial Authorisation. It is also an offence to implement a substantial amendment to a CTIMP without a favourable ethical opinion, or fail to provide pharmacovigilance reports, or to fail to notify the REC of urgent safety measures or the early termination or conclusion of the trial.

9.120 It is also an offence to provide false or misleading information to a recognised REC in the course of an application for an ethical opinion relating to a CTIMP or when giving a notice of amendment.

9.121 Where a REC receives information suggesting that a criminal offence may have been committed, it should proceed as in paragraph 9.111.

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**Good Clinical Practice inspections**

**Co-operation with investigations**

9.122 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 REC operations manager for discussion as appropriate with senior operational management at NRES. With the permission of the REC operational manager, the REC should co-operate fully. The REC should not under any circumstances undertake its own investigations.

9.123 The REC should co-operate fully if asked to assist with criminal investigations. The REC operational manager should be kept informed.

**Transfer of main REC responsibility**

9.124 The responsibilities of main REC for an ongoing study (or research tissue bank or database) may be transferred to another REC in the following circumstances:

(i) The main REC ceases to operate.

   In this case the REC operational manager should make arrangements for all the business of the REC to be taken over by a successor REC or RECs.
(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 main REC no longer has legal recognition for a particular type of study.

The REC operational manager should transfer main REC responsibility for these studies to other *appropriately recognised REC(s)*.

(iv) The main REC requests that responsibility for a study is transferred to another REC.

This applies only to *non-CTIMPs*. A main 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 amendment (e.g. to include participants lacking capacity). Such requests should be considered by the REC operational manager. 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.
Section 10: Research databases

General policy

10.1 Organisations responsible for the management of research databases anywhere in the UK may apply for ethical review of their arrangements for collection, storage and use of data, including arrangements for release of non-identifiable data for analysis by external researchers.

10.2 Ethical approval is required under GAfREC 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.

10.3 However, there is no general requirement for research databases to apply for ethical review under the Research Governance Framework for Health and Social Care or GAfREC.

10.4 REC approval 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 application to both the National Information Governance Board’s Ethics and Confidentiality Committee (NIGB ECC) 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 clients. (For detailed guidance on such applications, see paragraphs 13.68-13-111).

10.5 Applications for ethical review by research databases will therefore normally be made on a voluntary basis. However, application may have benefits by facilitating programmes of research using information on human subjects without a need for specific project-based applications. Applicants may seek generic ethical approval extending to specific projects undertaken using the data, subject to conditions agreed with the REC.

Defining a research database

10.6 The following paragraphs set out how NRES defines a research database for the purpose of the specific arrangements established for ethical review of research databases. It should be noted that the term “research database” may be used in other research contexts where application for ethical review as a research database is not appropriate.

10.7 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.
10.8 “Research purposes” in this context refers to analysis of data to answer research questions in multiple projects.

10.9 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.

10.10 Personal information may include data from images, as well as the images themselves.

10.11 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. Where such data is made available to researchers alongside samples for analysis, this constitutes a research database. However, for the purposes of ethical review it is considered to be part of a “research tissue bank” (RTB); application for ethical review should be made under the RTB scheme and the ethical issues relating to the data considered as part of an over-arching review of the research resource (see Section 11).

10.12 In summary, the research database application scheme 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 ethical review of research databases

10.13 Applications for ethical 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.

10.14 Standard procedures for booking and submission apply to such applications (see Section 1).

10.15 It is recommended that applicants apply to a flagged REC for review of research databases (see paragraph 1.7-1.15).

Validation

10.16 The normal validation criteria in paragraph 1.45 do not apply. 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 submitted electronically from IRAS to RED\(^{17}\) together with all supporting documents. (The checklist in IRAS indicates which documents are mandatory.)

ii. All relevant sections and questions have been completed and submitted;

iii. The application form has been electronically authorised in IRAS by the applicant (the Data Controller) and by the Data Custodian.

iv. Short curriculum vitae (a maximum of two pages is recommended) have 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 data subjects, copies of all information sheets and consent forms have been enclosed.

\(^{17}\) Or exceptionally in another electronic format – see paragraph 1.39.
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 1.46 apply.

10.17 RECs will normally only review databases established by organisations within the UK. However, applications related to non-UK databases may be accepted for review where the database plans to collect data relating to UK participants.

**Process of ethical review**

10.18 The process of ethical review will 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. Standard letters are modified slightly in RED to use the appropriate terminology for research database applications.

10.19. Where an unfavourable opinion is issued, the usual options for further ethical review described in Section 7 of SOPs will apply.

10.20. Substantial amendments to the terms of ethical approval for a database should be reviewed under the procedures in Section 5 of SOPs in the same way as substantial amendments to specific research projects. The appropriate Notice of Substantial Amendment form in IRAS should be used.

**Summary of issues for ethical review**

10.21 RECs undertaking ethical review of Research Databases should note the following general guidance on issues to be considered in applications:

- Purpose and value of the Database; why is this resource needed, how will it add value to existing sources of data in this 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 ethical approval

Approval for the Research Database team

10.22 Where a favourable opinion is given, this will give ethical 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 data subjects to process their personal data, unless exceptionally approval from the NIGB ECC is also obtained to process identifiable data without consent (see paragraph 10.4 and Section 13). 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

10.23 Applicants may also seek generic approval on behalf of external researchers receiving non-identifiable data to undertake valuable scientific studies. 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 by external researchers subject to conditions (see paragraph 10.27).

10.24 In this context, “external researchers” means researchers outside 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.

10.25 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 approval must not receive data in identifiable form or be able to identify subjects 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 further project-specific application should be made for ethical review.

10.26 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 ethical approval

10.27. Where ethical approval is given, the main REC should issue a set of approval conditions appropriate to Research Databases, normally including the following:

(a) Approval is given for a period of 5 years, which may be renewed on consideration of a fresh application.

(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 (with the exception of student research below doctoral level) 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 extracts:
   
   • Research must be conducted in circumstances such that data subjects are not identifiable to external researchers. Data extracts 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 ethical 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 main 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) An annual report should be provided to the REC using the specific template for research databases on the NRES website. The report should list all projects for which access to data has been given in the previous year, and summarising developments in the management of the resource. The main REC may request additional reports on the management of the database at any time.

(i) Substantial amendments should be notified to the main REC using the appropriate Notice of Substantial Amendment form in IRAS. The following should always be notified as substantial amendments
- 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 ethical approval;
- Appointment of a new Data Controller;
- Any other significant change to the location, management or governance of the database.

(j) The main 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.

(k) The main 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.

(l) Plans to close the database should be notified to the main 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 ethical approval is not transferable.

10.28 The REC has the discretion to modify these conditions or to attach other approval conditions as appropriate to the application. A template for the approval conditions (SL-AC4) is published on the NRES website and is available in RED. Where additional conditions are minor changes, for example to information sheets, rather than ongoing conditions relating to the governance of the database, these may be inserted in the opinion letter rather than SL-AC4.

10.29 Ethical approval may be given for a period of up to 5 years and will be renewable (see paragraphs 10.35-10.38).
Site-specific issues

10.30 SSA is not required for Research Database applications. The ethical review applies to the management of the database as a whole, including arrangements made with collaborators. There is no requirement for specific ethical approval for Data Collection Centres who provide data under the terms of a supply agreement between their organisation and the database. DCCs are not regarded as research sites for the purpose of the Research Governance Framework. However, local collaborators at Data Collection Centres within the NHS will require internal permission from their NHS care organisation to collect and supply data relating to NHS patients.

NHS management permission

10.31 Under the Research Governance Framework, there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

10.32 Research permission is also not required by collaborators at DCCs as these are not regarded as research sites.

10.33 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.

10.34 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 ethical approval. Where the data is received in non-identifiable form and the research is covered by the terms of generic ethical approval for the database, no further REC application is required but the database should list the project in its annual report to the REC.

Renewal of approval

10.35 Ethical approval for Research Databases is given for 5 years initially, but may be renewed for further periods of 5 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.

10.36 Procedures for renewal at the 5 year point are as follows:

(a) The Data Controller should provide the latest annual progress report by the due date, together with an updated version of the original application form and supporting documentation taking into account changes during the intervening period - this documentation should be submitted to the original REC (or another REC appointed to manage ongoing business if the original REC is no longer in operation);
(b) The Co-ordinator should issue a reminder about the need to submit the renewal documentation 3 months prior to the due date - all documentation in respect of the renewal of approval will be managed under the original REC Reference number;

(c) If the documentation in (a) is not received by the due date, the Co-ordinator should issue a further reminder and notify the Data Controller that the approval will lapse if it is not received within a further month;

(d) The renewal documentation should be reviewed at the next available full meeting of the REC. The Data Controller should be invited to attend.

(e) The REC may issue one written request for further information following the meeting;

(f) Assuming the REC is content to renew the approval, a renewal letter should be issued. The REC should aim to issue the renewal within 40 days of receipt of the renewal documentation, excluding time taken by the Data Controller to respond to one request for information. An overall deadline of 60 days will apply to the renewal application.

(g) Pending issue of the renewal letter, the previous ethical approval will remain in place;

(h) Renewed approvals will normally be for a further period of 5 years, backdated to the end of the previous 5 year period.

10.37 Exceptionally, if 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.

10.38 Before terminating ethical approval, the REC should first write to the Data Controller setting out its concerns and allowing opportunity for further representations to be made.
Section 11: Research involving human tissue

Statutory provisions

11.1 Detailed guidance on the provisions of the Human Tissue Act 2004 relating to research involving human tissue is at Annex H. 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.

11.2 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 H. The Scottish Government has issued separate guidance on how the principles of the HT Act apply to Scottish research generally. 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

11.3 The general policy from NRES is that the NHS REC system should:

- Provide ethical review of research using human tissue collected, stored and used within the UK as required by legislation and GAfREC.

- Undertake ethical 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 ethical review of research involving human tissue

England, Wales and Northern Ireland

11.4 Under the HT Act and the HT Regulations, researchers in England, Wales and Northern Ireland will legally require ethical 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 H).
• 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 H).

• Analysing human DNA in material from the body of a living person (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 H).

• 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 19-20 of Annex H).

11.5 The HT Regulations provide that, where ethical approval 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 REGs 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, Social Services and Public Safety in Northern Ireland. (For health-related research this means any REC which is part of the UK Health Departments’ Research Ethics Service under GAfREC.)

11.6 These provisions mean that, in general, researchers requiring ethical 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 GAfREC. RECs should accept any application requiring ethical approval under the Act.

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Scotland

11.7 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) Regulations 2004, 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 GAfREC in Scotland and England.
11.8 The Human Tissue (Scotland) Act 2006 does not require ethical 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.

Ethics and compliance with the law

11.9 When reviewing research involving human tissue, the role of the REC is to give an ethical opinion 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 committee 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.

11.10 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 ethical 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. The Human Tissue Authority (HTA) Code of Practice on Consent gives advice on questions to be considered in relation to the use of existing holdings in research. RECs should take compliance with this advice into account in a proportionate way in discussion with applicants.

Applications for ethical approval

11.11 There are two possible routes to obtaining ethical approval for research involving storage or use of human tissue or analysis of DNA:

(i) Application for approval of a specific project using the normal REC application form (see paragraphs 11.13-11.18). 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 paragraphs 9.10-9.11).

(ii) Application for approval of a research tissue bank (RTB), which may confer generic ethical 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 ethical approval (see paragraphs 11.19-11.32). Such approval may be given for a period of up to 5 years and will be renewable. A storage licence will be
required from the HTA for banks storing relevant material in England, Wales or Northern Ireland.

11.12 The same options apply where ethical approval:

- Is required by the HT Act in England, Wales or Northern Ireland in order to confer exemption from licensing or consent provisions (see paragraph 11.4)
- Is required by Departmental policy under research governance systems anywhere in the UK (broadly speaking, wherever the research involves collection of the tissue of NHS patients or use of previously collected tissue from which past or present NHS patients could be identified), or
- Is not required by law or policy as the research involves material which is outside the definition of “relevant material”, but is sought on a voluntary basis (for example, research involving plasma, serum, DNA or cell lines).

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Project-based applications

11.13 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 ethical approval from a REC.
(f) Research involving use of stored tissue from a research tissue bank, which has ethical approval from a REC, but (a) the terms of the approval do not extend to generic approval for projects receiving tissue from the bank (see paragraph 11.30(c)), or (b) 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 is not ethically approved.
(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.

11.14 Project-based applications should be made using the normal REC application form and 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 ethical 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 ethical review under departmental policy or on a voluntary basis, but not seeking ethical 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 Scotland A REC.

In Scotland, non-CTIMPs seeking ethical 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 if necessary (see paragraph 11.7).

11.15 “Participants” 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.

11.16 Applications should be reviewed in accordance with normal procedures. Standard policy on approval conditions applies to the review (see paragraphs 3.23-3.28).

11.17 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 by Co-ordinators. Nor is it acceptable to submit substantial amendments to approved projects in order to use tissue for another project with a different set of research questions.

11.18 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 (assuming it is given a favourable opinion), 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 a favourable opinion, 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 HTA for a licence.

• The researcher may hold on to the tissue without a licence under the original REC approval provided it is being held as a record of the completed research project, for example to verify research data. Storage for this purpose without a licence should continue for no longer than necessary. If the tissue continues to be stored without a licence for the purpose of any other research project, further ethical approval should be sought using either the project-specific or RTB application process.

Applications for ethical review of research tissue banks

11.19 Subject to paragraph 11.21, organisations responsible for the management of research tissue banks (RTB) anywhere in the UK may apply for ethical 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 ethical approval or for which ethical approval is pending.

11.20 Tissue banks storing human tissue for use in as yet unspecified research must obtain a licence from the HTA (except in Scotland). There is no requirement for tissue banks to obtain ethical approval under the HT Act or under NHS research governance systems or GAfREC. Applications will therefore be made on a voluntary basis, but ethical approval for a bank may have benefits by facilitating programmes of research without a need for individual project-based ethical approval.

11.21 Under arrangements being established in Scotland, each Health Board will have a research tissue bank, which will be accredited by Healthcare Improvement Scotland. With the exception of these banks, no other applications for REC review of research tissue banks should be made by researchers within NHS Scotland. Researchers working on NHS Scotland premises will be expected to utilise the accredited Health Board bank.
11.22 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/data relating to UK participants.

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Application form for RTB
11.23 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.

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Booking, allocation and validation of RTB applications
11.24 New applications should be booked via CAS and will normally be allocated to one of the panel of flagged RECs (see paragraph 1.7-1.15).

11.25 The normal validation criteria in paragraph 1.45 do not apply. RTB applications should meet the following validation criteria:

(a) The RTB application form has been correctly completed in IRAS and submitted electronically from IRAS to RED\textsuperscript{18} together with all supporting documents. (The checklist in IRAS indicates which documents are mandatory.);

(b) All relevant sections and questions have been completed;

(c) The application form has been electronically authorised by the applicant and, where applicable, by the Designated Individual;

(d) 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 fresh 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 in England, Wales or Northern Ireland has already obtained a licence from the HTA, a copy of the licence should be enclosed. (It is not mandatory to have obtained the licence before applying for ethical review.);

(h) Where an unfavourable opinion has been given to a previous application related to the same RTB, the additional criteria in paragraph 1.46 apply.

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\textsuperscript{18} Or exceptionally in another electronic format – see paragraph 1.39.
**Site-specific issues**

11.26 SSA is not required for RTB applications. The ethical review applies to the management of the tissue bank as a whole, including arrangements made with collaborators. There is no requirement to apply for ethical approval for individual research sites 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 ethical review for RTB applications**

11.27 The process of ethical 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.

11.28 Where an unfavourable opinion is issued, the usual options for further review described in Section 7 will apply.

11.29 Substantial amendments to the terms of ethical approval for a RTB (see paragraph 11.31(f)) should be reviewed under the procedures in Section 5 in the same way as substantial amendments to specific research projects.

**General guidance on ethical review of RTBs**

11.30 RECs undertaking the ethical review of RTBs should note the following general guidance:

- The review should focus particularly on the following ethical 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.
• Ethical review should be proportionate, balancing the need to protect the safety, rights and well being of donors with the need to facilitate research of value to society as a whole.

• In England, Wales and Northern Ireland the ethical review should generally complement the process of licensing by the HTA rather than duplicate it. 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. (This guidance does not apply in Scotland where there is no licensing process.)

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Approval conditions for RTBs

11.31 The main 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 5 years, which may be renewed following further review based on progress reports (see paragraph 11.33).

(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 Authority renews the licence, modifies the licensing conditions or revokes the licence, or of any change of Designated Individual.

(c) Where the applicant has applied for generic ethical 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 be satisfied that the research has been subject to scientific critique, is appropriately designed in relation to its objectives and (with the exception of student research below doctoral level) 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 ethical approval and any other conditions required by the RTB.

(Note: It is not mandatory for RTBs to apply for generic ethical approval on behalf of end users. A RTB may opt to require all researchers receiving tissue to apply individually to a REC for ethical approval using the project-based application form. Where generic ethical approval is sought, it is open to the REC either to give simple ethical approval to the Bank only or to give an approval which includes generic approval for end users.)

(d) 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 main REC may request access to this record at any time.

(e) An annual report should be provided to the REC, using the specific template for RTBs available on the NRES website. The report should list all projects for which tissue has been released in the previous year and summarise any developments in the management of the resource. The main REC may request additional reports on the management of the RTB at any time.

(f) Substantial amendments (see paragraph 11.29) should be notified to the main REC using the appropriate Notice of Substantial Amendment form in 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) The main 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.
(h) The main 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 main 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 ethical approval is not transferable.

11.32 The REC has the discretion to modify these conditions or to attach other approval conditions as appropriate to the application. A template for the approval conditions (SL-AC3) is published on the NRES website and is available in RED. Where additional conditions are minor changes, for example to information sheets, rather than ongoing conditions relating to the governance of the RTB, these may be inserted in the opinion letter rather than SL-AC3.

11.33 Research conducted using tissue provided by a RTB under the conditions in paragraph 11.31(c) will be considered to have ethical approval from the REC under the terms of the ethical 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.

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Renewal of approval

11.34 Ethical approval for RTBs is given for 5 years initially, but may be renewed for further periods of 5 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.

11.35 Procedures for renewal at the 5 year point are as follows:

(a) The RTB manager should provide the latest annual progress report by the due date, together with an updated version of the original application form and supporting documentation taking into account changes during the intervening period - this documentation should be submitted to the original REC (or another REC appointed to manage ongoing business if the original REC is no longer in operation);

(b) The Co-ordinator should issue a reminder about the need to submit the renewal documentation 3 months prior to the due date - all documentation in respect of the renewal of approval will be managed under the original REC Reference number;

(c) If the documentation in (a) is not received by the due date, the Co-ordinator should issue a further reminder and notify the RTB manager that the approval will lapse if it is not received within a further month;
(d) The renewal documentation should be reviewed at the next available full meeting of the REC. The RTB manager should be invited to attend.

(e) The REC may issue one written request for further information following the meeting;

(f) Assuming the REC is content to renew the approval, a renewal letter should be issued. The REC should aim to issue the renewal within 40 days of receipt of the renewal documentation, excluding time taken by the RTB manager to respond to one request for information. An overall deadline of 60 days will apply to the renewal application.

(g) Pending issue of the renewal letter, the previous ethical approval will remain in place;

(h) Renewed approvals will normally be for a further period of 5 years, backdated to the end of the previous 5 year period.

11.36 Exceptionally, if 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.

11.37 Before terminating ethical approval, the REC should first write to the RTB manager setting out its concerns and allowing opportunity for further representations to be made.

Project applications relating to tissue held by an approved RTB

11.38 Where a researcher applies for review of a specific project involving tissue held by an approved RTB, the REC reference number for the RTB should be cited in the application. It is recommended that the application should be submitted to the main REC for the RTB (“the tissue bank REC”). This will facilitate the ethical review because the REC will already be familiar with the nature of the tissue and the conditions under which it has been collected. 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.

Standard letters for RTB applications

11.39 Changes have been made to standard letter templates on RED for use with RTB applications. The changes include modifications to terminology (for example, amending references to “study”, “Chief Investigator” etc) and the guidance given to the applicant (for example, explaining that SSAs are not required). For guidance on the issue of approval conditions with a favourable opinion letter, see paragraphs 11.30-11.31.
Transitional arrangements for RTBs with an existing ethical approval

11.40 Any ethical approval given by a REC to a RTB prior to 31 October 2006 lapsed on 30 October 2008. A new application may be made to a REC at any time.

Import and export of human tissue

11.41 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.

11.42 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 is ethically approved.

11.43 The consent provisions of the HT Act do not apply to tissue that has been imported.

General policy on ethical review of research outside the UK

11.44 It is not the role of the REC system 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 ethical opinion on activities carried out outside the UK. It is more appropriate that the activities are subject to ethical review in the country concerned, taking into account 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.

11.45 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
11.46 Under the Regulations made under the HT Act, researchers undertaking projects using imported tissue require ethical approval from a REC where the material will be held on unlicensed premises during the project. Where a researcher requires ethical 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 GAfREC and relating solely to the storage or use of imported tissue for research. The guidance in paragraph 1.92 applies to such applications.

11.47 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

11.48 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 may 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

11.49 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.
Section 12: Research involving adults unable to consent for themselves

Introduction

12.1 This section of SOPs sets out the procedures governing ethical 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) Regulations 2004 as amended (“Clinical Trials Regulations”)
- Non-CTIMPs, where the legal position differs across the UK with important implications for the process of ethical review.

A. Clinical trials of investigational medicinal products (CTIMPs)

12.2 The inclusion in CTIMPs of adults unable to consent for themselves is governed by the provisions of the Clinical Trials Regulations and the Adults with Incapacity (Scotland) Act 2000. The research provisions of the Mental Capacity Act 2005 do not apply to the conduct of CTIMPs.

New applications

12.3 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.

12.4 When booking the application with the Central Allocation System (CAS), the applicant should declare that the trial involves adults unable to consent for themselves.

12.5 CAS should allocate the application to a REC, which is both:

- Recognised for the purpose of reviewing CTIMPs in patients (Type 3 recognition), and where possible:
- Flagged for the purpose of reviewing research involving adults unable to consent for themselves (see paragraph 12.20).

(Note: Phase 1 trials cannot include adults unable to consent for themselves, as one of the requirements of Part 5 of Schedule 1 to the Regulations is that there are grounds for expecting that administering the investigational medicinal product will produce a benefit to the subject. This is incompatible with the definition of a Phase 1 trial under the
REGULATIONS. Therefore trials involving adults unable to consent would never be reviewed by Type 1 recognised RECs.)

12.6 Where the trial is to be conducted at one or more sites in Scotland, and the Chief Investigator is professionally based in Scotland, it should be allocated to “the Ethics Committee” constituted by Scottish Ministers under the Adults with Incapacity (Scotland) Act 2000. This committee is currently the Scotland A REC. If the Chief Investigator is based outside Scotland, the application may be allocated to any other REC, which is both recognised and flagged for the purpose of reviewing research involving adults unable to consent for themselves.

Ethical review

12.7 The main 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 Part 5 of Schedule 1 to the Clinical Trials Regulations. These include provisions for informed consent to be given by the subject’s legal representative. A definition of “legal representative” for this purpose is given in Part 1 of Schedule 1.

12.8 NRES has issued an information paper on “Informed Consent in Clinical Trials of Investigational Medicinal Products”, outlining the relevant provisions of Schedule 1. This is available at http://www.nres.nhs.uk/applications/guidance/clinical-trials/.

12.9 The ethical review of a CTIMP involving adults with incapacity in Scotland is governed by the provisions of the Clinical Trials Regulations. The provisions of the Adults with Incapacity (Scotland) Act 2000 are superseded by the Clinical Trials Regulations where any conflict arises.

Expert advice

12.10 The main REC is required by Regulation 15(7) of the Clinical Trials Regulations to obtain advice before giving its opinion on any trial involving adults unable to consent for themselves. The procedures set out in paragraphs 2.50-2.57 should be followed.

B. Research other than CTIMPs

Mental Capacity Act 2005 (England and Wales)

Scope

12.11 Sections 30-34 of the Mental Capacity Act make detailed provision relating to research involving living adults aged 16 or over who are unable to consent for
themselves. The Act applies in England and Wales only. The provisions of Sections 30-34 do not apply to CTIMPs. The MCA does not apply to research involving the deceased. The Human Tissue Acts govern the post-mortem removal, storage and use of organs and tissue.

12.12 The application of these provisions is not limited to medical and biomedical research, health-related research or research taking place within the NHS. It applies potentially to research in the context of social care and in any other context where participants could lack capacity to give informed consent.

Timetable for implementation of the Act

12.13 The provisions of sections 30-33 of the Act came into force on 1 October 2007. Any new research starting on or after 1 October 2007 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. (Guidance on transitional arrangements for ethically approved research starting prior to 1 October 2007 is given in paragraphs 12.32-12.36).

12.14 The Mental Capacity Act 2005 (Loss of Capacity during Research Project) (England) Regulations 2006 and equivalent Regulations made by the National Assembly for Wales (NAW) also came into force on 1 October 2007. These Regulations (referred to collectively in these SOPs as the “Loss of Capacity Regulations”) are made under Section 34 of the Act. They provide in certain circumstances for continuation of research involving data or material, which has been taken with consent from a person who subsequently loses capacity before the research ends. The Regulations apply only where the research started before 1 October 2007 and the person concerned initially consented to participate before 30 March 2008.

Intrusive research

12.15 For the purposes of sections 30-33, “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 approval from the REC and the NIGB Ethics and Confidentiality Committee (see Section 13);

(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 H), 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.

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Requirements for approval by an appropriate body

12.16 There are two types of approval for research under the Act:

- Approval under section 30 to undertake any “intrusive research” where the participants include one or more adults unable to consent for themselves (“Section 30 approval”).
- Approval under the Loss of Capacity Regulations to undertake research using data or material obtained before a participant lost capacity (in a study which started before 1 October 2007 and where the participant gave consent before 30 March 2008) (“Section 34 approval”).

12.17 Both types of approval 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 (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).
12.18 All NHS RECs established under GAfREC 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 Act. The Ministry of Defence RECs are also recognised for research within their remits.

12.19 An approval by any appropriate body in England or Wales applies to the conduct of the research in both England and Wales.

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Flagged RECs

12.20 Although legally any REC established under GAfREC in England and Wales may approve research under the MCA, NRES has established a panel of flagged RECs for research involving adults unable to consent for themselves. (For general guidance on flagged RECs, refer to paragraphs 1.7-1.15.)

12.21 The panel includes RECs in Scotland and Northern Ireland for the purposes of research taking place in those countries. (For guidance on research taking place in more than one UK country, see paragraph 12.57.)

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New applications for section 30 approval

12.22 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 Act, an adult is a person aged 16 or over.

12.23 When booking the application with the Central Allocation System (CAS), the applicant should declare that the study plans to include adults unable to consent for themselves.

12.24 CAS will normally allocate the application to a REC in England or Wales, which is flagged for review of research involving adults unable to consent for themselves. Research taking place in England or Wales only should normally 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 or Wales.

12.25 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 12.57.

12.26 If a researcher seeks to book a new application involving adults unable to consent for themselves directly with a REC (other than the Social Care REC), the Coordinator should decline the booking and advise booking through CAS.
12.27 Before giving an opinion on any new application for section 30 approval, a REC should obtain expert advice on any clinical, ethical or psychosocial problems that may arise in relation to including adults unable to consent for themselves. The advice may be provided either by a member of the REC, a co-opted member or a referee under the procedures set out in paragraphs 2.50-2.57. The member or referee concerned should be a person with professional expertise relevant to the treatment or care of the population to which the research relates.

12.28 The Co-ordinator should register the application on RED as an application for section 30 approval and use the modified standard letters generated. Where a favourable opinion is issued and section 30 approval is given to include adults unable to consent for themselves, the opinion letter should include the following additional paragraph:

“Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.”

12.29 It should be noted that there could be cases where section 30 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. The REC would need to be satisfied that appropriate changes had been made to the inclusion criteria and recruitment procedures.

12.30 Where either an unfavourable opinion is given, or a favourable opinion is given but section 30 approval is withheld, the opinion letter should include the following additional paragraph:

“Mental Capacity Act 2005

The committee did not approve this research project for the purposes of the Mental Capacity Act 2005. The research may not be carried out on, or in relation to, a person who lacks capacity to consent to taking part in the project.”

12.31 The Chief Investigator may either appeal or submit a further application under the procedures in Section 7. Any appeal or new application will normally be allocated to a flagged REC.

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adults unable to consent for themselves until approval has been obtained. Where such participants have been included unlawfully from 1 October 2008, the REC cannot give retrospective approval.

12.33 Applications for section 30 approval may be made in either of the following ways:

Option 1: Supplementary application

- A supplementary application for section 30 approval may be submitted directly to the main REC that originally approved the study, provided that this REC is established under GAfREC in England or Wales. Supplementary applications should be booked so that an agenda slot at a full REC meeting can be reserved.

- A Notice of Substantial Amendment form should be submitted, together with Part B Section 6 of the REC application form in IRAS, a revised protocol incorporating procedures for complying with sections 32-33 of the Act and an information sheet for consultees. Any application not including these documents is invalid.

- The REC should review the supplementary application according to the normal SOPs for new applications. It should be reviewed at a full meeting with at least 7 members. The REC should communicate a final decision to the Chief Investigator within 60 days; the clock may stop once to request any further information or clarification.

- The Coordinator should register the application as a supplementary application for Section 30 approval and use the modified standard letters generated in RED.

- If the REC gives section 30 approval, the Coordinator should insert in the favourable opinion letter the additional text at paragraph 12.28.

- If section 30 approval is not given, the text at paragraph 12.30 should be used. The research may for the time being continue on the basis of the original favourable opinion, but it would be unlawful for any further intrusive research to be carried out on or in relation to adults unable to consent for themselves from 1 October 2008. There is no appeal procedure but the researcher may submit a new full application to a flagged REC under option 2 below. If the main REC is itself a flagged REC, the researcher may submit another supplementary application to the main REC, or a new full application to another flagged REC.

- There is no requirement to carry out further SSAs.

Option 2: New application

- A new application may be booked via CAS and submitted to another REC (“the second REC”), which should normally be a flagged REC. The REC application form should be completed in full.

- The second REC should review the application in the same way as any new application for section 30 approval (see paragraphs 12.22-12.31).

- If an unfavourable opinion is given and/or the application for section 30 approval is rejected, the opinion from the original main REC remains in place. The research may continue but it would be unlawful for any further intrusive research.
to be carried out on or in relation to adults unable to consent for themselves from 1 October 2008. The researcher may however submit a further application to the second REC or another flagged REC under the procedures in Section 7.

- If an unfavourable opinion is given, the research should be regarded as no longer ethically approved. It would be unlawful for any further intrusive research to be carried out on or in relation to adults unable to consent for themselves from 1 October 2008. The researcher may appeal or submit a further application under the procedures in Section 7.

- There is no requirement to carry out further SSAs.

12.34 Where application for section 30 approval relates to research previously approved by Scotland A REC (previously the MREC for Scotland Committee A) or a HSC REC in Northern Ireland, the applicant must submit either a supplementary or a new application to a REC in England and Wales (“second REC”). If submitting a supplementary application, the applicant should also provide a copy of the original REC application form and related correspondence for information, as the second REC will have no prior knowledge of the research in this instance. The second REC should confine its review to whether the statutory criteria for section 30 approval are met in England and Wales.

12.35 Where existing research was originally approved by an ethics committee not established under GAfREC (e.g. social care research approved by a university committee), it was not required to comply with sections 30-33 until 1 October 2008. To obtain section 30 approval, a new application should be made as under Option 2 above.

12.36 Where existing research was underway without approval from any ethics committee, it was required to comply with sections 30-33 from 1 October 2007. Applications may continue to be accepted after 1 October 2007 but the researcher should suspend research procedures involving adults unable to consent for themselves until approval has been obtained from a REC. Where such participants have been included unlawfully from 1 October 2007, the REC cannot give retrospective approval.

Applications for section 34 approval

12.37 Where existing research has a favourable opinion from a NHS REC in England and Wales, application for section 34 approval should be made to the main REC for the study by submitting a Notice of Substantial Amendment together with the following:

- The supplementary information form for section 34 approval (form MCA2), which is published on the NRES website.

- A revised protocol incorporating procedures for complying with the Loss of Capacity Regulations.

- An information sheet for consultees.
12.38 Where the research has an existing favourable opinion from Scotland A REC or a HSC REC in Northern Ireland, the applicant should also provide a copy of the original application form and related correspondence (see paragraph 12.34).

12.39 Any application not including all the above documents is invalid.

12.40 The Co-ordinator should register the substantial amendment on RED as an application for section 34 approval. The application should be processed according to the normal procedures for substantial amendments. A decision should be communicated to the applicant within 35 days of receipt of a valid application.

12.41 Review of the amendment should include consideration of whether the research may continue to use data or material from participants who have lost capacity, having regard to the Loss of Capacity Regulations. If approved, the favourable opinion letter should include the following additional paragraph:

"Mental Capacity Act 2005"

I confirm that the committee has approved the protocol for this research to be carried out in relation to a person who [consents] [consented] to take part in the project prior to 31 March 2008 but, before the conclusion of the project, loses capacity to consent to continue to take part in it. I confirm that the committee is satisfied that there are reasonable arrangements in place for ensuring the requirements of the Regulations made under section 34 of the Mental Capacity Act 2005 are met."

12.42 If the amendment is not approved, the researcher may submit a modified amendment in the usual way.

12.43 Where an application for section 34 approval relates to research with approval from an ethics committee not established under GAfREC (e.g. social care research approved by a university committee), or with no previous ethical approval, a full application for ethical review should be submitted to a REC together with Form MCA2. If the REC gives a favourable opinion and section 34 approval, the additional paragraph above should be added manually to the favourable opinion letter.

Sources of guidance on the Mental Capacity Act


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.

12.45 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.

12.46 An on-line toolkit on research involving adults lacking capacity, which was developed for NRES by a joint team from the University of Leicester and the University of Bristol, is available via the NRES website.

12.47 The Medical Research Council and the British Psychological Society have published detailed practical guidance for researchers on the inclusion of adults unable to consent for themselves. Additional guidance for social scientists has been developed by SCIE and is available on the SCIE and NRES websites.

12.48 Summaries of the statutory criteria for section 30 and section 34 approval are available on the NRES website.

**Adults with Incapacity (Scotland) Act 2000**

12.49 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”).

12.50 Where any non-CTIMP is to be conducted at one or more sites in Scotland, the application should be booked through CAS. Under the AWI Act, the research must be approved by “the Ethics Committee” constituted by Scottish Ministers under Regulations made under the Act. This committee is currently the Scotland A REC. CAS should allocate all such applications to Scotland A REC, which will review the application under section 51 of the AWI Act.

12.51 The guidance relating to expert advice in paragraph 12.27 does not apply. The constitution of the Scotland A REC is determined by Regulations made under the AWI Act.

12.52 For procedures relating to research to be conducted in other UK countries as well as Scotland, see the guidance in paragraph 12.57.

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**Northern Ireland**

12.53 There is at present no specific legislation in Northern Ireland governing the inclusion in research of adults unable to consent for themselves. The legal position is determined solely by the common law.

12.54 Where any non-CTIMP is to be conducted at sites in Northern Ireland only, the application should be booked through CAS and allocated to one of the Health and Social Care (HSC) RECs.
12.55 The HSC REC should obtain expert advice before giving an opinion on the application. The guidance in paragraph 12.27 should be followed.

12.56 For procedures relating to research to be conducted in other UK countries as well as Northern Ireland, see the guidance in paragraph 12.57.

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### Research other than CTIMPs: research conducted in different UK countries

12.57 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.

<table>
<thead>
<tr>
<th>Countries where sites located</th>
<th>Application process</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and/or Wales only</td>
<td>Apply to any flagged REC in England or Wales.</td>
</tr>
<tr>
<td>Scotland only</td>
<td>Apply to Scotland A REC.</td>
</tr>
<tr>
<td>Northern Ireland only</td>
<td>Apply to any HSC REC in Northern Ireland.</td>
</tr>
<tr>
<td>England and Wales</td>
<td>Apply to any flagged REC in England or Wales.</td>
</tr>
<tr>
<td>England/Wales and Scotland</td>
<td>Two applications should be made:</td>
</tr>
<tr>
<td></td>
<td>1. The England/Wales application should be made to a flagged REC in England or Wales.</td>
</tr>
<tr>
<td></td>
<td>2. The Scotland application should be made to the Scotland A REC.</td>
</tr>
<tr>
<td></td>
<td>Separate versions of the REC application form in IRAS should be submitted with separate REC reference numbers.</td>
</tr>
<tr>
<td>Area</td>
<td>Application Details</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>England/Wales and Northern Ireland</td>
<td>The applications will be reviewed separately having regard to the relevant legislation. Any favourable opinion will apply only to England/Wales or Scotland respectively. Different opinions may be given.</td>
</tr>
<tr>
<td></td>
<td>Apply to any flagged REC in England or Wales. Only one application is required. The main REC will seek advice from a HSC REC on issues relating specifically to participants in Northern Ireland. Any advice will be incorporated in the main review.</td>
</tr>
<tr>
<td>Scotland and Northern Ireland</td>
<td>Apply to Scotland A REC. Only one application is required. The main REC will seek advice from a HSC REC on issues relating specifically to participants in Northern Ireland. Any advice will be incorporated in the main review.</td>
</tr>
</tbody>
</table>
| England/Wales, Scotland and Northern Ireland | Two applications should be made:  
1. Application for England/Wales/Northern Ireland should be made to a flagged REC in England or Wales.  
2. Application for Scotland should be made to the Scotland A REC. Separate versions of the REC application form in IRAS should be submitted with separate REC reference numbers.  
The applications will be reviewed separately having regard to the relevant legislation. Any favourable opinion will apply only to England/Wales/Northern Ireland or Scotland respectively. Different opinions may be given.  
The main REC in England or Wales will seek advice from a HSC REC on issues relating specifically to participants in Northern Ireland. Any advice will be incorporated in the main review. |
Site-specific assessment

12.58 SSA is required for any new application involving adults unable to consent for themselves (except for applications for section 30 approval under the MCA submitted under the transitional arrangements in paragraph 12.33). The normal procedures for SSA in Section 4 of the SOPs apply. Where the site is outside the NHS, the SSA should be undertaken by an appropriate NHS REC.

Addition of new sites

12.59 The usual SOPs apply to addition of new sites, except where the research is extended to a new country for the first time. The following situations should be noted:

- Where research is extended to England and Wales for the first time, a new application should be made to a flagged REC in England or Wales.
- Where research is extended to Scotland for the first time, a new application should be made to Scotland A REC.
- Where research is extended to Northern Ireland for the first time, a substantial amendment should be notified to the main REC. An amended protocol should be submitted, setting out the proposed recruitment procedures in Northern Ireland, together with a copy of the information sheet(s) and assent form(s) to be used. The main REC should consult an HSC REC in Northern Ireland on the amendment.

Substantial amendments to include adults lacking capacity

12.60 Where intrusive research is already underway and it is proposed to include adults unable to consent for themselves for the first time, a notice of substantial amendment should be submitted to the main REC together with the following:

- Part B Section 6 of the REC application form
- Revised protocol;
- Information sheets and consultation/consent/assent forms (as appropriate, depending on whether the study is a CTIMP or non-CTIMP and which UK jurisdiction(s) are involved).

12.61 Where the amendment relates to a CTIMP, the usual SOPs apply to the review. Where it relates to a non-CTIMP, a 60 day timescale applies to the review and the
REC may stop the clock once to request further information or clarification in the same way as for a new application. The amendment should be reviewed at a full committee meeting.

12.62 Expert advice should be available to the REC when reviewing such amendments (see paragraph 12.27). Co-ordinators should ensure that at least one member who has attended training in adults lacking capacity is involved in the review. Where the main REC is not flagged and expertise is not available on the committee, advice should be sought from a flagged REC.

12.63 For non-CTIMPs being conducted in England and Wales, the Co-ordinator should register the amendment in RED as an application for section 30 approval under the MCA. The opinion letter should include the additional paragraph in paragraph 12.28 or 12.30 as applicable.

12.64 For non-CTIMPs being conducted in Scotland, the notice of substantial amendment requires review by the Scotland A REC under the Adults with Incapacity (Scotland) Act. The following guidance should be noted:

- If Scotland A REC is not already the main 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 12.60.

- If the main REC for the study is another REC in Scotland (“first REC“), the NOSA should be submitted to Scotland A REC rather than the first REC. Scotland A REC will consult the first REC before giving its opinion. If Scotland A REC gives a favourable opinion of the amendment, it will take over main REC responsibility for the study; all REC documentation should be transferred by the first REC. If it gives an unfavourable opinion, main REC responsibility remains with the first REC.

- If the study is being conducted both in Scotland and England/Wales, the amendment should be submitted for separate review in both jurisdictions. If Scotland A REC give a favourable opinion, it will assume main REC responsibility for Scotland. Responsibility for the study in England/Wales remains with the main REC in that jurisdiction.
Section 13: Communication with other regulators and review bodies

General policy

13.1 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 ethical review. Applicants are encouraged to submit applications at the same time but may apply in sequence if they prefer.

13.2 The Research Ethics Service aims to collaborate closely with regulatory bodies to ensure that the approvals process as a whole is robust, efficient, proportionate and facilitative. In particular, 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.

13.3 It is the responsibility of the sponsor to ensure where necessary that a research study has appropriate regulatory approval as well as a favourable ethical opinion before it starts. It is not necessary for evidence of regulatory approval to be provided to the REC before it confirms the final ethical opinion. The Chief Investigator is requested to provide evidence of regulatory approval for the REC’s records as soon as this is available, but it is not the responsibility of the REC to follow this up proactively.

13.4 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 amendments should be submitted during the review process where appropriate (see paragraph 5.11).

13.5 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

13.6 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 ethical opinion. An application for CTA should be made to the licensing authority, which is the Medicines and Healthcare products Regulatory Agency (MHRA). The requirement for CTA replaces the previous statutory requirements under the Medicines Act 1968 to obtain a Clinical Trials Certificate (CTC), a Clinical Trials Exemption (CTX), a Doctor and Dentists Exemption (DDX) or approval to conduct a Clinical Trial of a Marketed Product (CTMP).

Memorandum of Understanding

13.7 A Memorandum of Understanding (MoU) between the MHRA, NRES, GTAC and AAPEC (version 2, June 2010) sets out the respective roles and responsibilities of MHRA and recognised RECs in relation to CTIMPs, and agreed procedures for collaboration and communication. The MoU is published on the NRES website and includes contact points for use by RECs and operational managers.

Roles and responsibilities

13.8 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. It 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 sufficient understanding of the scientific background and the safety issues to be able to give an ethical opinion. In particular, the committee should make an ethical 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 ethical review must also ensure that the potential risks and benefits of the trial are fully and clearly explained in the participant information sheet.

13.9 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

13.10 The Clinical Trials Regulations provide for sharing of relevant information on CTIMPs between ethics committees and the MHRA. Where appropriate, the REC may seek clarification of the status of the CTA application from the MHRA Clinical Trials Unit. The REC may also draw to the attention of CTU, and seek its advice on, significant concerns about the safety of the trial that have not been resolved by information provided by the applicant. Emails should be sent to
clintrialhelpline@mhra.gsi.gov.uk marked “URGENT: REC correspondence for Head of CTU”. SL16 may be used. A response will be sent within two working days. This procedure should only be used to raise specific safety issues. For general scientific advice, the REC should either seek further information from the sponsor or consult its own referees.

13.11 The Chief Investigator should provide the main REC with a copy of the letter from the MHRA confirming the CTA. Any remarks made by the MHRA should be noted by the main REC. Where the main REC receives the letter after the issue of a favourable opinion, the Co-ordinator should ensure that the letter is reviewed at the next available sub-committee or committee meeting so that any remarks made by the MHRA can be noted. If necessary, the committee may seek further information or clarification from the Head of CTU (see paragraph 13.10). Exceptionally, it may review its opinion in the light of any new scientific or safety issues arising from the MHRA assessment that have a bearing on the ethical acceptability of the trial (see paragraph 13.28). For further guidance about communication with MHRA on safety issues arising after the trial has started, see paragraph 9.64.

Trials subject to EAG/CHM assessment

13.12 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 ethical 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.

13.13 CTIMP applications should indicate whether or not the trial is subject to EAG/CHM assessment. If so, the application should indicate the current status of the application for CTA and, where applicable, any changes made to the proposed trial in the light of the expert advice. Any relevant correspondence with the MHRA should be enclosed with the application.

13.14 If the applicant indicates that the trial is not subject to EAG/CHM assessment and the REC has reason to question this, it may seek advice from the Clinical Trials Unit under the procedures in paragraph 13.10.

13.15 The Regulations allow for submission of applications to the MHRA and the ethics committee in parallel. This applies to trials subject to EAG/CHM assessment in the same way as other trials. Where the applications are made in parallel the REC application should be accepted for review if it is valid. However, the following procedures apply exceptionally to the ethical review:

(i) Where the committee decides to issue a provisional opinion, the further information requested from the applicant may include a report on the outcome of the MHRA application, which may well be available to the sponsor at this stage. The clock stops until all the information requested has been received. (Note: The responsibility to respond to the request lies with the Chief Investigator as the applicant for ethical review, but the sponsor has the overall responsibility
for ensuring the committee is appropriately informed and may make arrangements with the CI to reply to the committee directly.)

(ii) If CTA has by now been confirmed, the CI or sponsor should forward a copy of the MHRA letter to the committee together with any relevant correspondence.

(iii) If grounds for non-acceptance have been raised, the CI or sponsor should forward a copy of the MHRA letter to the committee. The applicant may withdraw the ethics application and re-submit having made the changes required by the MHRA. Alternatively, if he/she continues with the ethics application, the sponsor should include with the further information requested by the committee a summary of how the issues raised by MHRA have been addressed.

(iv) If the outcome of the MHRA application is not yet available, the clock remains stopped until it is. Once the committee has received a complete response to the request for further information, including the outcome of the MHRA application, the clock re-starts. The committee should conclude its review and issue the final opinion as soon as possible. Further clarification on specific areas of concern may be sought from the MHRA at this stage if necessary.

Notifying MHRA of the REC opinion for upload to EudraCT

13.16 The main REC is required by the Clinical Trials Regulations to notify the MHRA of the final opinion, whether favourable or unfavourable, so that it can be entered on EudraCT. The MHRA is notified automatically through its access to RED.

13.17 MHRA is also required to enter the reasons for an unfavourable opinion in EudraCT, using a checklist of standard fields prescribed by the European Commission (see Annex E). This checklist is available within RED. Co-ordinator should provisionally complete the checklist within 2 working days of issuing the unfavourable opinion letter. The REC operational manager should check that the fields have been completed appropriately, amend if necessary in discussion with the Co-ordinator and sign off for notification to MHRA in RED within a further 3 working days. Further operational guidance has been issued by the NRES Head of Operations.

13.18 This process also applies to unfavourable opinions given following appeal. Where the same application is given more than one unfavourable opinion, the MHRA will update EudraCT according to the latest opinion. Where a trial is given a favourable opinion following appeal, the MHRA will change the status of the opinion in EudraCT.

Compliance with Good Clinical Practice

13.19 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 subjects 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 sites of pharmaceutical companies, contract research organisations, non-commercial organisations, investigational trial sites, clinical laboratories, GCP archives and other facilities involved in CTIMPs.
13.20 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

13.20 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 may require verification of the application documentation and correspondence held by the main REC. Any request from the GCP Inspectorate to inspect documentation will be made in writing to the Co-ordinator of the main REC, copied to the REC operational manager. The main REC should normally facilitate the inspection. Any concern on the part of the REC about the inspection should be referred to the REC operational manager. If the matter cannot be resolved locally with the GCP Inspectorate, the REC operational manager should notify senior operational management at NRES, who will contact the GCP Operations Manager at the MHRA.

Notifying MHRA of compliance issues in CTIMPs

13.21 RECs should draw serious concerns about compliance issues in CTIMPs to the attention of the REC operational manager under the procedures for notifying possible serious breaches (see paragraph 9.107-9.118). In consultation with senior operational management at NRES, the REC operational manager 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 at GCP.SeriousBreaches@mhra.gsi.gov.uk.

13.22 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 site without a favourable opinion for the site or the Principal Investigator.
- Provision of false or misleading information to the main REC in relation to an application for ethical opinion or notification of substantial amendment.
- Implementation of a substantial amendment 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.
13.23 Consideration should also be given to notifying the MHRA where a pattern emerges of repeated minor breaches of GCP or the protocol.

13.24 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 REC operational manager. When writing direct to the MHRA, the REC should copy the notification to the operational manager. The operational manager should ensure that the NRES Head of Operations is kept informed.

13.25 All reports received by MHRA will be acknowledged. Feedback will be provided to senior operational management at NRES on the findings of any resulting inspections or investigations. NRES will arrange for relevant RECs and operational managers to be notified.

13.26 Where the MHRA takes regulatory or enforcement action in relation to the conduct of a CTIMP, senior operational management at NRES will be notified and a copy of the relevant inspection report provided. NRES will arrange for relevant RECs and operational managers to be notified and to receive a copy of the inspection report.

13.27 Copies of inspection reports will not be routinely disclosed to RECs. However:

- Any report on a Phase 1 trial site will be provided to the REC or RECs with assigned responsibility for SSA for the site;
- 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 main REC, REC operational manager or senior operational management at NRES.

**Review of opinion on a CTIMP**

13.28 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 ethical opinion given previously.* However, the main 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.

13.29 Where appropriate, the Chair should write to the Head of the Clinical Trials Unit by email explaining the Committee’s concerns in full. SL16 may be used. 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 site or facilities.

The CTU will consider what action should be taken in relation to the CTA and will notify the main REC accordingly. The action taken could include request to the sponsor for further information, request for amendment of the trial, or suspension or termination of the CTA. Further information or clarification may be sought from the main REC about its concerns. The CTU may seek separate advice from referees.

13.30 The MHRA will directly inform the main 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 main 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 main REC.

MHRA - clinical investigations of medical devices

Regulatory requirements for medical devices

13.31. 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).

13.32 Under the Directives, no medical device (with the exception of custom-made devices) may be placed on the EU market without 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. Responsibility for CE Marking lies with accredited Notified Bodies in each Member State.

Clinical investigations of non-CE marked devices

13.33 In order to demonstrate compliance with the requirements for 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.

13.34. The manufacturer must notify any such clinical investigation to the Competent Authority of the Member State(s) in which the investigation is being performed. In the UK, the notification is made to the MHRA Devices Division.

13.35. The requirement to notify a clinical investigation to MHRA also applies where a study of a non-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 [http://www.mhra.gov.uk/Howweregulate/Devices/index.htm](http://www.mhra.gov.uk/Howweregulate/Devices/index.htm) or the NRES guidance on approval for medical devices research.

13.36. Where notification of a clinical investigation is made, MHRA has 60 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 in the form of a Notification of No Objection. The REC should be provided with a copy of the Notice of No Objection when available, either in the course of the ethical review or following the issue of a favourable opinion.

13.37. 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. The ethical opinion can be obtained in parallel with the Competent Authority Notification.

Roles and responsibilities

13.38. The MHRA assessors review applications to ensure that sufficient, 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.

13.39. The main 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.

13.40. The main REC is responsible for addressing other ethical 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 sites or publication of study results.

Research involving CE marked devices

13.41 If a manufacturer conducts a study with a 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 CE marking, notification of a clinical investigation to the MHRA is required under the Medical Devices Regulations in the same way as for non-CE marked devices. The arrangements in paragraphs 13.32-13.37 apply.

13.42 Where studies involve 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 GAfREC.

Communication with MHRA on medical devices research

13.43 Guidance on communications between RECs and MHRA Devices Division has been agreed by NRES and the MHRA and is published on the website. The guidance includes contact points.

13.44 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.

13.45 When reviewing a clinical investigation requiring regulatory approval, the main 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 ethical 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 (susanne.ludgate@mhra.gsi.gov.uk) copied to the Regulatory Affairs Manager for Devices (daniella.smolenska@mhra.gsi.gov.uk) with the subject line “URGENT: REC correspondence for Clinical Director”.

13.46 MHRA Devices Division is notified of REC opinions on clinical investigations electronically through access to RED.

13.47 When reviewing a study of a 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

13.50 The administration of radioactive substances in the United Kingdom is governed by the Medicines (Administration of Radioactive Substances) Regulations 1978 (MARS), made under the Medicines Act 1968. Regulation 2 of MARS requires that any doctor or dentist wishing to administer radioactive medicinal products to humans should hold a certificate issued by Health Ministers. MARS also established the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise Health Ministers on the issuing of certificates. ARSAC also provides advice on related matters, specifically those associated with radiological safety. The Secretariat to ARSAC is provided by a support unit within the Health Protection Agency.

13.51 Where research involves the administration of radioactive substances, additional to those provided as part of routine care, an ARSAC research certificate must be held at each research site where administrations take place. The certificate is site, procedure and holder specific. The issue of a certificate (“ARSAC research certificate”) is required for any research involving administrations additional to those carried out by the certificate holder as part of normal clinical care.

13.52 Arrangements for collaboration between ARSAC and the Research Ethics Service have been agreed in a Memorandum of Understanding between NRES and the Health Protection Agency.

Roles and responsibilities

13.53 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, taking into account 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 site;
• potential variations in clinical practice between research sites.

13.54 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.

13.55 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 ethical issues.

Applications to ARSAC

13.56 Application to ARSAC is a two-stage process, comprising:

• A Preliminary Research Assessment (PRA) form, submitted by the sponsor’s representative
• A Research Certificate Application (RCA) form, submitted by the local certificate-holder at the site if required.

13.57 The PRA form may be submitted electronically from IRAS as soon as the REC application has been booked and submitted. Sponsors are encouraged to submit the applications in parallel 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 ethical review where appropriate.

13.58 A Research Certificate Application (RCA) form may be submitted by the local certificate-holder as soon as both the REC application and the PRA form have been submitted. The form is submitted off-line, combined with other components of the ARSAC certificate application giving further details of the site and certificate-holder and including all necessary signatures.

ARSAC review process and communications with the REC

13.59 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 office for information.

13.60 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 certificates for individual sites.
13.61 Once ARSAC has received satisfactory responses from the sponsor’s representative to any issues raised in the initial assessment, individual certificates will normally be issued within 2 working days of receipt of RCA forms unless further site specific information is required. These do not normally require consultation with ARSAC members and will be processed within the ARSAC Support Unit.

13.62 Certificates are not be copied to the REC office. It is the responsibility of the sponsor and the R&D office at the site to check that a certificate is in place before the study starts.

**REC review process**

13.63 For all applications involving radioactive substances, the Co-ordinator should copy the REC’s provisional and final opinion letters to the ARSAC Support Unit.

13.64 In framing a request for further information, the REC should take into account 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.

13.65 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.

13.66 Where a provisional opinion letter 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.

13.67 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.

**National Information Governance Board (NIGB)**

**Statutory requirements**
13.68 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.

13.69 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".

13.69 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.

13.70 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.

13.71 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 NIGB

13.72 The National Information Governance Board (NIGB) is established under Section 250A of 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 NIGB provides leadership and promotes consistent standards for information governance across health and social care.

13.73 The NIGB has statutory responsibility for advising the Secretary of State on applications for Section 251 approval, both in relation to medical research and other medical purposes. NIGB delegates this activity to its Ethics and Confidentiality Committee (ECC).

13.74 The NIGB ECC also advises the HFEA on applications for authorisation under the Human Fertilisation and Embryology (Disclosure of Information for Research Purposes) Regulations 2010.

Review responsibilities
13.75 Where applications are made both to the NIGB ECC 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**

13.76 The ECC 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.

13.77 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.

13.78 In considering the public interest, both the ECC 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.

13.79 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 NIGB ECC**

13.80 The ECC 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**.

13.81 The ECC 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 1998, the Human Rights Act 1998 and the Common Law Duty of Confidentiality.

13.82 The ECC 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.

13.83 The ECC 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**

13.84 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.

13.85 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 NIGB ECC – standard procedures

13.86 The REC office should send a copy of the REC’s provisional and final opinion letters to the NIGB ECC Secretariat by email. The ECC Secretariat may request a copy of responses from the applicant to the REC where these could be relevant to the ECC’s review.

13.87 The NIGB ECC Secretariat will send a copy of its provisional and final outcome letters, together with the applicant’s responses, to the REC office by email.

13.88 Where the REC gives a favourable opinion, it should include as a condition of its approval a requirement for approval from NIGB ECC before the research can start. The NIGB ECC will include a similar condition with its approvals.

13.89 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. Correspondence with the ECC Secretariat should be sent to eccapplications@nhs.net.

Resolving differences on key issues

13.90 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. Such discussion may take place by email or telephone. The REC Co-ordinator should co-ordinate discussion with the ECC Secretariat, involving the Chair and lead reviewer(s) as appropriate. The outcome of any telephone discussions should be recorded. The REC operational manager should be kept informed.

13.91 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.

13.92 Where agreement on key issues cannot be reached, the matter should be reported to the NRES Head of Operations, 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 NRES Head of Operations will proceed in consultation with the OREC Manager for Wales.

Procedures following rejection of application by ECC

13.93 Where the ECC 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 Notice of Substantial Amendment should be submitted. Where the initial application for ethical review is still in process, the changes should be notified to the REC by letter.

Application to the REC only – is application also required to NIGB ECC?

13.94 In this scenario, the applicant indicates in the IRAS Project Filter that the research requires ethical review by a REC but does not require an application to the NIGB ECC.

13.95 Where it appears to the REC that the research may require application to the NIGB ECC, the REC should seek advice on the matter from the ECC Secretariat directly by email. The ECC Secretariat will advise the researcher directly and inform the REC Co-ordinator of the outcome. Where application to the ECC is required, the standard procedures in paragraphs 13.86-13.93 above will apply. The REC should make it a condition of a favourable opinion that NIGB ECC approval is obtained.

Mental Capacity Act 2005

13.96 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 12).

13.97 This definition of intrusive research (see paragraph 12.15) 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 ECC 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 ECC 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

13.98 Where the researcher is applying for both REC and ECC 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).

13.99 In considering whether it is justified to set aside the common law duty of confidentiality, both ECC 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.

13.100 The usual procedures relating to communication between the REC and the ECC apply in such cases (see paragraphs 13.86-13.93).

13.101 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 ECC

13.102 Where the ECC 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 Notice of Substantial Amendment should be submitted with appropriate supporting documentation (see paragraph 12.60). Where the initial application is still in process, the changes to the application and supporting documentation should be submitted to the REC by letter.

13.103 The REC should copy all correspondence relating to the application for MCA approval to the ECC.

Procedures following rejection of MCA application by the REC

13.104 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 ECC and a Notice of Substantial Amendment to the REC. The guidance in paragraphs 13.86-13.93 applies to the dual processing of these applications.

Amendments to approved research
Notifying amendments to NIGB ECC

13.105 Where research is underway with ECC approval, the applicant is required to notify the ECC of any amendments to the activity set out in the original application. Notification may be made by letter at the time of the amendment or as part of the annual review report to NIGB ECC if that is due within the next month. The scale and type of amendment will determine whether the project can continue under the existing approval or needs to be re-considered by the ECC.

Amendments to research with dual approval

13.106 Following REC review of a substantial amendment, the REC should send to the ECC Secretariat a copy of the Notice of Substantial Amendment together with the opinion letter. There is no need to provide copies of other correspondence or supporting documentation unless requested.

13.107 The ECC Secretariat will send to the REC office a copy of any letter from the applicant notifying amendments to the research, together with any further correspondence. Where the ECC has simply noted the amendment for information, the Secretariat will notify the REC accordingly.

13.108 Where either review body takes, or expects to take, a different position to the other on an amendment, the guidance in paragraphs 13.90-13.93 applies.

Substantial amendment to study with REC opinion only

13.109 Very exceptionally, a substantial amendment 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.

13.110 Where the applicant is in the process of applying to the ECC for section 251 approval in parallel with the Notice of Substantial Amendment, the guidance in paragraphs 13.86-13.93 applies.

13.111 Where the substantial amendment appears to require section 251 approval but the applicant is not planning to apply to the ECC, the guidance in paragraphs 13.94-13.95 applies.
Section 14: Storage and retention of documentation

Statutory requirements

14.1 Schedule 2 to the Clinical Trials Regulations (as amended) requires that the main 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.

14.2 There is no statutory requirement to retain documentation relating to applications that are withdrawn prior to giving an opinion.

14.3 The Regulations do not exclude retention of documentation for longer than the specified period.

14.4 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

14.5 The policy from NRES is that the provisions of the Clinical Trials Regulations should apply to all specific research studies reviewed by RECs.

14.6 In addition, documentation should be retained on all invalid applications for at least 1 year from the date of invalidation.

14.7 Wherever possible, documentation should be submitted by applicants electronically and should be retained by RECs in electronic rather than paper format. Documentation received or sent on paper (e.g. correspondence with ink signatures) should be scanned to PDF and uploaded to RED. All documentation relating to an application will be stored in RED where possible. Where documentation is stored electronically, there is no requirement for long-term storage in another format; additional paper copies may be destroyed. Temporary paper files may be held by REC offices for applications and other business currently being processed, but should be destroyed once no longer needed (for example, once the opinion on a new application or substantial amendment has been issued, or other correspondence has been concluded).

14.8 Signed final copies of the minutes of full REC meetings and sub-committee business should be retained indefinitely. Where electronic versions are available, paper copies may be destroyed. Draft versions of the minutes should be destroyed once the final

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19 Following introduction of electronic submission for all applications – see paragraph 1.39.
version has been ratified and signed, together with any written comments submitted by members or manuscript notes taken during meetings.

14.9 Any remaining historic paper files, which have not been scanned to RED or archived to CD or other electronic media, will normally be destroyed as soon as possible following the “retention date” (see paragraph 14.11). However, REC operational managers may exceptionally advise the REC office to continue to retain documentation where appropriate, for example in the case of studies that are still the subject of complaints, investigations, insurance claims, or significant public or media interest. Where this applies, the need for further retention should be reviewed at least annually by the operational manager.

14.10 Where paper records are destroyed in accordance with this policy, they should be shredded and disposed of as confidential waste.

14.11 Operational management guidance on archiving historic paper files to CD or other electronic media is issued by the NRES Head of Operations.

14.12 Electronic records of studies will be retained indefinitely.

**Defining the retention period for paper documentation**

14.13 The “retention date” for a specific study is the date following which any remaining paper files on a study will normally be destroyed. The retention date is defined as in the table below.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Retention date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invalid application</td>
<td>12 months from the date of sending SL3 (application considered invalid)</td>
</tr>
<tr>
<td>Application withdrawn by Chief Investigator or sponsor prior to final opinion</td>
<td>3 years from the date of sending SL26 (acknowledging notification of withdrawal)</td>
</tr>
<tr>
<td>Application deemed withdrawn by REC due to failure to respond to provisional opinion</td>
<td>3 years from the date of sending SL13 (application deemed withdrawn)</td>
</tr>
<tr>
<td>Study abandoned prior to commencement</td>
<td>3 years from the date on which the REC is notified (see paragraph 9.9)</td>
</tr>
<tr>
<td>Study terminated early by sponsor</td>
<td>3 years from the date of early termination (as notified by the sponsor)</td>
</tr>
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<td>----------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study halted following termination of favourable opinion by REC (non-CTIMPs only)</td>
<td>3 years from the date of sending SL43 (termination of opinion)</td>
</tr>
<tr>
<td>Study halted following termination of regulatory approval by MHRA or other relevant body</td>
<td>3 years from the date of the termination of regulatory approval</td>
</tr>
</tbody>
</table>

**Study completed**

3 years from the date of the conclusion of the study (as notified by the sponsor in the end of study declaration)

14.14 Further operational management guidance for RECs on the closure of studies is issued by the NRES Head of Operations.

**Study documentation to be retained by the main REC**

14.15 Except where stated, the following guidance applies retrospectively to studies previously reviewed as well as future studies.

14.16 The following documents should be retained by the main 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 amendment and all accompanying documentation (including any revised versions provided during ethical review)
- Notifications of minor amendments
- 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
• 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 amendments, progress/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.

14.17 There is no requirement to retain the following:
• Quarterly or six monthly safety reports submitted on CTIMPs under previous SOPs
• Reports of non-UK SUSARs or serious adverse events
• Reports of UK SUSARs preceding the most recent annual safety report and line listing
• Earlier versions of the Investigator’s Brochure superseded by the latest version, except that the version submitted with the initial application should be retained
• Written comments provided by REC members prior to meetings, or notes made at meetings, following ratification of the minutes (see paragraph 2.81).

Study documentation to be retained by SSA RECs

14.18 SSA RECs undertaking SSA for non-NHS sites should retain the SSI Form, accompanying documentation and any correspondence relating to the SSA until the retention date for the study.

14.19 SSA RECs should also retain, until the retention date, documentation relating to SSA undertaken for NHS sites in CTIMPs prior to the transfer of responsibility to NHS R&D offices in April 2009. This includes “locality assessments” undertaken by Local Research Ethics Committees for CTIMPs reviewed by Multi-Centre Research Ethics Committees prior to the issue of version 1 of the SOPs in March 2004.

14.20 There is no requirement to retain any documentation relating to SSA or locality assessment undertaken for NHS sites in non-CTIMPs prior to April 2009.

14.21 Where initial ethical review was undertaken by more than one REC prior to March 2004, there is no requirement to retain any documentation relating to ethical review undertaken by RECs other than the assigned main REC for the study.
Research tissue banks and research databases

14.22 Documentation relating to REC approved research tissue banks and research databases should be retained indefinitely. Where a resource ceases to operate, the tissue bank or database manager should inform the REC what arrangements will be made for continuing custody and oversight of the samples/data. Records should be retained by the REC for reference in the event of further applications by the institutions assuming responsibility for the resource; or, in the case of mergers with other resources, for linkage with records of reviews undertaken by other RECs.
ANNEX A: Index to standard letters and forms

Validation of application

SL1  Acknowledgement of a valid application (study requiring SSA)
SL1A Decision on SSA exemption for non-NHS site(s)
SL2  Acknowledgement of a valid application (study not requiring SSA)
SL3  Invalid application
SL4  Request for advice of referee prior to the meeting

Decision at initial meeting of the REC

SL5  Favourable opinion
SL6  Unfavourable opinion
SL7  Provisional opinion with request for further information
SL8  Provisional opinion pending consultation with referee

Further consideration and confirmation of final opinion

SL9  Request for advice of referee following the meeting
SL10 Further information requested following consultation with referee
SL11 Further information received but not a complete response
SL12 Reminder for further information
SL13 Further information not provided, application considered withdrawn by the REC
SL14 Favourable opinion following consideration of further information
SL15 Unfavourable opinion following consideration of further information

Correspondence with MHRA

SL16 Correspondence with MHRA

Site-specific assessment

SL17 Valid application for SSA
SL18 Invalid application for SSA
SL19 SSA – notification of no objection
(for use where RED cannot be used to notify outcome of SSA electronically)

SL20 SSA – notification of objection

SL23 Unfavourable opinion for site following objection from site-specific assessor

SL23A Acknowledgement of notice of substantial amendment to add new non-NHS site or PI in a CTIMP

SL23B Confirmation of favourable opinion for new NHS site following notice of substantial amendment in a CTIMP

SL23C Extension of favourable opinion to non-NHS site following SSA

Projects outside the remit of a REC

SL24 Pre-application advice on project not requiring REC review

SL25 Ethical opinion on research not requiring REC review

Withdrawal of application by researcher

SL26 Application withdrawn by researcher

Amendments

SL27 Acknowledgement of a valid notice of a substantial amendment

SL28 Invalid notice of a substantial amendment

SL29 Acknowledgement of substantial amendment to CTIMP notified for information only

SL30 Acknowledgement of minor amendment to a CTIMP

SL31 Acknowledgement of minor amendment to a non-CTIMP

SL32 Favourable opinion of a substantial amendment

SL33 Unfavourable opinion of a substantial amendment

SL34 Favourable opinion of a modified amendment

SL35 Unfavourable opinion of a modified amendment

Appeals

SL36 Confirmation of appeal by NRES Head Office
SL36A  Appeal disallowed
SL36B  Arrangements for appeal

**Monitoring of approved research**

SL37  Acknowledgement of annual progress report
SL38  Reminder for annual progress report
SL39  Acknowledgement of declaration of end of study
SL40  Acknowledgement of final research report
SL41  Reminder for final research report
SL42  Notice of Intention to Suspend or Terminate a Favourable Opinion (non-CTIMP)
SL42A Suspension or termination of favourable ethical opinion (non-CTIMP)
SL43  Notification of possible misconduct
SL44  Acknowledgement of documentation provided following favourable opinion with conditions

**Publication**

SL45  Notification to CI of publication of research summary

**Standard approval conditions**

SL-AC3 Approval conditions (research tissue banks)
SL-AC4 Approval conditions (research databases)


**After ethical review - guidance for sponsors and investigators**

SL-AR1  Clinical trials of investigational medicinal products
SL-AR2  Other specific research projects

Forms for use by Co-ordinators

SF2   Confidentiality undertaking by observer at REC meeting

Forms for use by applicants (CTIMPs)

A. Notification of amendment form (European Commission form)
B. Declaration of the end of a clinical trial (European Commission form)
C. Annual progress report form (NRES)
D. Safety report form (NRES)

Forms for use by applicants (non-CTIMPs)

E. Notice of substantial amendment (NRES)
F. Declaration of the end of a study (NRES)
G. Annual progress report form (NRES)
H. Report of serious adverse event (NRES)

Forms A and E are available within IRAS.

Form B is Annex 3 to ENTR/CT1 issued by the European Commission. The form can be downloaded from the EudraCT website, see:

All other forms are issued by NRES and can be downloaded from
www.nres.nhs.uk/applications/afterethicalreview.

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ANNEX B: 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 subjects 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 13.34). 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.

Detailed guidance on how to apply for a Clinical Trial Authorisation (CTA) is published on the MHRA website at the following link:

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/IsaclinicaltrialauthorisationCTArequired/index.htm
The guidance includes advice on when a CTA is required, together with an algorithm to help sponsors and investigators to decide whether or not a study is a CTIMP.

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ANNEX C: Notification of substantial amendments to CTIMPs

The sponsor of a clinical trial of an investigational medicinal product (CTIMP) is required to notify substantial amendments to the MHRA and/or the main REC.

The sponsor must indicate on the European Commission notice of amendment form whether the request is for:

- Authorisation by the competent authority, or
- Favourable opinion from the ethics committee, or
- Both authorisation and a favourable ethical opinion.

Where a substantial amendment 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 an amendment meets the criteria for a substantial amendment, and if so whether it requires authorisation and/or an ethical opinion. However, sponsors may wish to take account of the following general guidance, which has been agreed between NRES and the MHRA.

Amendments 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

Amendments normally requiring a favourable ethical opinion only

- Significant\(^{20}\) 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 site)
- Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial
- Significant increase to the radiation exposures to subjects from the protocol
- Change of insurance or indemnity arrangements for the trial

\(^{20}\) “Significant”, i.e. likely to affect to a significant degree the safety or physical or mental integrity of trial subjects or the scientific value of the trial, or otherwise significant.
• 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 of Principal Investigator at a trial site

• Addition of new trial sites not listed with the original request for authorisation and REC application

• Change to the definition of a trial site

• Any other significant change to the conduct or management of the trial at particular trial sites

• Early closure or withdrawal of a site

• Any other significant change to the terms of the original REC application.

Amendments normally requiring both authorisation and a favourable ethical 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

• 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

• Change of the sponsor or sponsor’s legal representative

• Temporary halt of the trial or temporary halt at a trial site, and re-start of the trial following a temporary halt

• Change of the definition of the end of the trial.
Amendments not normally requiring notification as substantial amendments

- Changes to the identification of the trial (e.g. change of title)\textsuperscript{21}
- 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 to the numbers of participants planned in the UK as a whole or at individual trial sites, provided that there is no change to the total number of participants in the trial or the increase/decrease is insignificant in relation to the overall sample size
- Change in the documentation used by the research team to record study data (e.g. case report form or data collection form)
- Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis
- Changes to the research team other than to Chief or Principal Investigators
- Changes to contact details\textsuperscript{22}
- Changes to the internal organisation of the sponsor or persons to whom tasks have been delegated
- Changes to the logistical arrangements for transporting or storing samples
- Changes to technical equipment
- Inclusion or withdrawal of another Member State or third country
- Non-significant clarifications of the protocol
- Non-significant clarifications or updates of participant information documentation
- Corrections of typographical errors.

The issue of an updated Investigator’s Brochure or Summary of Medicinal Product Characteristics for the IMP is not itself regarded as a substantial amendment unless it includes changes that would meet the criteria for a substantial amendment. There is no requirement to provide the MHRA or main REC with updated versions of the Investigator’s Brochure or SMPC routinely or to seek authorisation or an ethical opinion.

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\textsuperscript{21} Sponsors are requested to notify the REC of this change for information only.

\textsuperscript{22} Sponsors are requested to notify the REC of changes to the contact details of the sponsor, sponsor’s main contact point, sponsor’s legal representative (if applicable) or Chief Investigator, for information only.
ANNEX D: Corrective procedures following a legally invalid ethical 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 trial was reviewed by a type 2 recognised committee and later extended to another domain without seeking further review by a type 3 committee;
   - The ethical review process did not comply with the requirements of Regulation 15 for expert advice on trials involving minors or adults with incapacity; or
   - The ethical review process breached the quorum requirements in Schedule 2, for example because the meeting was attended by fewer than seven members or by more than two co-opted members.

2. Such non-compliances are referred to in this annex as “invalid ethical opinions”. They will normally come to light as a result of an audit of the ethics committee undertaken by NRES 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 ethical opinion should initially be sent to the REC operational manager for the ethics committee 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 ethical opinion, following further review of the trial where appropriate;
   (ii) Notify the Clinical Trials Unit and the GCP Inspectorate of the non-compliance and the corrective action being taken by the Research Ethics Service; and
   (iii) Notify the sponsor and give advice about the action it should take.

4. The REC operational manager will notify and consult with the NRES Head of Operations and/or the Director of NRES before proceeding.

5. 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 non-recognised committee

5.1 If a Trial is submitted as a CTIMP and a favourable opinion is given by non-recognised committee:

(i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants, and prepare a new application for review by an ethics committee with appropriate recognition.

(ii) The REC operational manager should identify an appropriate committee, secure an early agenda slot and notify the sponsor of the submission arrangements.

(iii) The sponsor should submit a Notice of Substantial Amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.

(iv) When a new favourable opinion is obtained, the sponsor should submit a further Notice of Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.

(v) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.

Trial submitted as a CTIMP and favourable opinion given by a committee without appropriate type of recognition

5.2 If a Trial is submitted as a CTIMP and a favourable opinion given by 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, and prepare a new application for review by an ethics committee with appropriate recognition.

(ii) The REC operational manager will identify an appropriate committee, secure an early agenda slot and notify the sponsor of the submission arrangements.

(iii) The sponsor should submit a Notice of Substantial Amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.

(iv) When a new favourable opinion is obtained, the sponsor should submit a further Notice of Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.

(vi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.
Trial submitted and ethically reviewed as a non-CTIMP, and it is later confirmed by MHRA it is a CTIMP

5.3 If a Trial is submitted and ethically reviewed as a non-CTIMP, and it is later confirmed by the MHRA that it is a CTIMP:

(i) The REC operational manager should liaison 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 ethical opinion.

Where the trial was 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 ethical opinion;

(v) The sponsor should submit a Notice of Substantial Amendment to the REC, enclosing an updated REC application form correctly identifying the study as a CTIMP and including the EudraCT number and Part B Section 1;

(vi) A copy of the CTA letter should be enclosed with the NOSA or forwarded as soon as available;

(vii) The NOSA and accompanying documentation should be reviewed by a sub-committee including at least the Chair and a pharmacist member;

(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 citing the EudraCT number, and the status of the study changed to a CTIMP in RED;

(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 NRES and MHRA;

Where the trial was reviewed by a non-recognised committee

(xi) The procedures under 5.1 apply.

Where the trial was reviewed by a committee without appropriate recognition for the type of CTIMP
(xii) The procedures under 5.2 apply.

**Trial with ethical opinion from a type ii committee extended to another domain without review by a type iii committee**

5.4 If a Trial with an ethical opinion from a type ii committee is extended to another domain without review by a type iii committee:

(i) The Director of NRES will seek early approval from UKECA in correspondence to change the terms of the ethics committee’s recognition to type iii for the purposes of this trial only.

(ii) Once UKECA approval is obtained, the operational manager will notify the Clinical Trials Unit and GCP Inspectorate of the non-compliance and the corrective action taken.

(iii) There is generally no need to notify the sponsor or for the trial to be suspended.

(iv) If, exceptionally, UKECA approval is not given, further corrective action should be taken in the same way as for a trial without an opinion from an appropriately recognised committee.

**Non-compliance with requirements of Regulation 15 or Schedule 2**

5.5 If a Trial is non-compliant with requirements of Regulation 15 or Schedule 2\(^2\):

(i) The REC operational manager should investigate further and consider whether there is any reason to be concerned about the safety or well-being of the trial subjects taking into account the nature and extent of the non-compliance.

Where no concerns arise:

(ii) The operational manager will make arrangements for the ethics committee to re-consider the application and confirm its opinion at a quorate meeting as soon as possible.

(iii) When the opinion is confirmed, the operational manager will notify the sponsor of the non-compliance and the corrective action taken, and arrange for revised documentation to be issued.

(iv) The operational manager will confirm to the Clinical Trials Unit that corrective action has been taken.

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\(^2\) These procedures assume that the non-compliance has come to light following issue of the ethical opinion. If the opinion has not yet been issued, the operational manager will advise the committee what steps to take in processing the application to ensure the opinion is valid.
Where, exceptionally, concerns arise about the safety or well-being of trial subjects:

(v) The sponsor should be notified immediately and advised to suspend all trial activity as soon as possible, except where this would be detrimental to health of participants, and prepare a new application for ethical review.

(vi) The sponsor should submit a Notice of Substantial Amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.

(vii) The REC operational manager will consider whether the new application should be reviewed again by the same committee or submitted to a different committee. The operational manager will identify an early agenda slot and notify the sponsor of the submission arrangements.

(viii) When a new favourable opinion is obtained, the sponsor should submit a further Notice of Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.

(ix) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.
ANNEX E: Notification of reasons for unfavourable opinion to the MHRA

1. The EudraCT database includes a list of prescribed fields to record the reasons for an unfavourable opinion given by an ethics committee on a CTIMP. (See European Commission document at http://ec.europa.eu/health/files/eudralex/vol-10/2010_10_14_final.pdf ). This information is available within the closed module of EudraCT to all Competent Authorities in EU Member States. It is not publicly available except in the case of paediatric clinical trials, for which the reasons will be published along with other details of the trial at www.ClinicalTrialsRegister.eu.

2. The checklist of fields in EudraCT is as follows:
   - Relevance of the clinical trial
   - Evaluation of the anticipated benefits and risks
   - Investigators and staff
   - Facility in a single-centre trial
   - All facilities in a multi-centre trial
   - Inclusion and exclusion criteria
   - Control group
   - Recruitment procedures
   - Participant Information Sheet and consent form and procedure
   - Measures to minimise pain, discomfort and fear
   - Insurance and/or indemnity (for liability) or no fault compensation in the event of injury or death attributable to the trial
   - Compensations (i.e. payments/rewards) to participants) to investigators
   - Agreement between sponsor and site relevant to compensations to participants or investigators
   - Inclusion of persons incapable of giving informed consent or other vulnerable populations
   - Data protection and confidentiality
   - Compliance with GCP
   - Fulfilment of administrative requirements
   - Other

3. The checklist is completed in RED by REC Co-ordinators when issuing an unfavourable opinion in a CTIMP and made available electronically to the MHRA (see paragraph 13.16-13.18 of SOPs).
ANNEX F: Format and content of Annual Safety Reports on CTIMPs

The ICH E2F guideline on Development Safety Update Reports, which establishes the standards for annual safety reports required under the EU Clinical Trials Directive, recommends that reports should adopt the format set out below. For each heading where information is available, the information should be presented concisely. Where no information is available or the section is not applicable, this should be stated.

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Title page

Executive Summary

1. Introduction
2. Worldwide marketing approval status
3. Actions taken in the reporting period for safety reasons
4. Changes to reference safety information
5. Inventory of clinical trials ongoing and completed during the reporting period
6. Estimated cumulative exposure
   6.1 Cumulative subject exposure in the development programme
   6.2 Patient exposure from marketing experience
7. Data in line listings and summary tabulations
   7.1 Reference information
   7.2 Line listings of serious adverse reactions during the reporting period
   7.3 Cumulative summary tabulations of serious adverse events
8. Significant findings from clinical trials during the reporting period
   8.1 Completed clinical trials
   8.2 Ongoing clinical trials
   8.3 Long-term follow-up
   8.4 Other therapeutic use of investigational drug
   8.5 New safety data related to combination therapies
9. Safety findings from non-interventional studies
10. Other clinical trial / study safety information
11. Safety findings from marketing experience
12. Non-clinical data
13. Literature
14. Other DSURs
15. Lack of efficacy
16. Region-specific information
17. Late-breaking information
18. Overall safety assessment
  18.1 Evaluation of the risks
  18.2 Benefit-risk considerations
19. Summary of important risks
20. Conclusions

Appendices to the DSUR

Title page
The title page of the DSUR should include the following information:

- DSUR number (reports should be numbered sequentially)
- Investigational drug
- Reporting period
- Date of the report
- Sponsor name(s) and address(es)
- Statement on the confidentiality of the information included in the DSUR
- A cautionary statement that the DSUR includes unblinded information, if applicable

Executive Summary
This section should provide a concise summary of the important information in the report, suitable for review by REC members as a stand-alone document.

The following information should be included in the Executive Summary:

- Introduction – report number and reporting period
- Investigational drug(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s)
- Estimated cumulative exposure of clinical trial subjects
- Marketing approval(s) (yes/no) – if yes, number of countries
- Summary of overall safety assessment (based on section 18 of the DSUR)
- Actions taken for safety reasons including significant changes to the IB
Conclusions

Further detailed guidance on each section of the DSUR is available within the ICH E2F guideline, available at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
ANNEX G: 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 site.

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 main 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.

3. Applicants must provide information to the main REC 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. In particular, applicants must show that:
   - the arrangements cover the research study concerned;
   - the sponsor, protocol authors, investigators/collaborators and, where applicable, Site 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 (see paragraph 1.45(d)).

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 the committee has 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. RECs should note that, 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. RECs should bear in mind that 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. The REC system may rely on the NHS research governance process for this purpose and it is not necessary for the applicant to provide documentary evidence of NHS indemnity with the application to the main REC. 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 sites, 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 site, 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 main REC with a clear statement of the policy for the trial on the application form, confirming that the 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 main 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, taking into account 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.

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Site-specific assessment at non-NHS sites

11. Except in the case of Phase 1 trials, applications for SSA at non-NHS sites should include evidence of insurance or indemnity cover for:

- the Contract Research Organisation (CRO) or Site Management Organisation (SMO) responsible for conduct of the study at the site;
- the Principal Investigator, including any GP or other independent practitioner recruiting private patients (see paragraph 12).

The position of independent practitioners

12. GPs are usually independent practitioners who provide services under contract with the primary care organisation (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 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 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 patients**, the NHS 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 ethical reviews or SSAs 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 ethical review or SSA involving patients in private practice 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 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 ethical 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-CE marked medical devices, or licensed medicines or 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.
ANNEX H: 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 11 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.cfm. The most important of these for the purpose of ethical 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. With the exception of 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.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/RegulatorySupportCentre/Training/Distancelearning/index.htm).
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 ethical review is required under NHS research governance systems and GAfREC.

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 1.12 below) 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 11.10 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 able to identify the tissue donor or be likely to be able to do so in future. 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 ethical approval to qualify for exemption from licensing (see paragraphs 25-27).

Table 1: Summary of legal requirements for consent to remove, store or use tissue or analyse DNA in bodily material for research purposes

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Consent legally required?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage or use of existing holdings</td>
<td>No</td>
</tr>
<tr>
<td>Analysis of DNA in existing holdings</td>
<td>No</td>
</tr>
<tr>
<td>Storage or use of imported tissue</td>
<td>No (but good practice for importer to seek evidence of consent – see HTA Code of Practice)</td>
</tr>
<tr>
<td>Storage or use of tissue from a deceased person who died more than 100 years ago</td>
<td>No</td>
</tr>
<tr>
<td>Storage or use of tissue from the living (not identifiable to the researcher)</td>
<td>No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)</td>
</tr>
<tr>
<td>Analysis of DNA in tissue from the living (not identifiable to the researcher)</td>
<td>No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)</td>
</tr>
<tr>
<td>Storage or use of tissue obtained from a deceased person who died less than 100 years ago</td>
<td>Yes</td>
</tr>
<tr>
<td>Storage or use of tissue from the living (identifiable to the researcher)</td>
<td>Yes</td>
</tr>
<tr>
<td>Removal of tissue from the living</td>
<td>Yes (under common law)</td>
</tr>
<tr>
<td>Removal of tissue from the deceased</td>
<td>Yes</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Analysis of DNA in tissue from the living (identifiable to the researcher)</td>
<td>Yes</td>
</tr>
<tr>
<td>Analysis of DNA in tissue obtained after 1 September 2006 from a deceased person who died less than 100 years ago</td>
<td>Yes</td>
</tr>
</tbody>
</table>

12. On consent practice, the HTA encourages informed and generic consent to use 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**

<table>
<thead>
<tr>
<th>The person</th>
<th>Who gives consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living adult, or living child(^1) with capacity and willing to make a decision</td>
<td>His/her own consent</td>
</tr>
<tr>
<td>Living child(^24) who lacks capacity to give consent or who has capacity but is unwilling to make a decision</td>
<td>A person with parental responsibility</td>
</tr>
</tbody>
</table>
| Deceased adult | (i) His/her own consent before death.  
(ii) If no prior consent by the deceased adult, the consent of a nominated representative.  
(iii) If no representative was appointed by the deceased person, a person in a qualifying relationship. |

\(^{24}\) The HT Act defines a child as a person under the age of 18.
### Deceased child

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>A person who had parental responsibility immediately before the child’s death.</td>
</tr>
<tr>
<td>(ii)</td>
<td>If no person had parental responsibility, another person in a qualifying relationship.</td>
</tr>
</tbody>
</table>

### Living adult who lacks capacity to give consent

See paragraph 15 below.

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:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>Spouse or partner (including civil partners)</td>
</tr>
<tr>
<td>(b)</td>
<td>Parent or child</td>
</tr>
<tr>
<td>(c)</td>
<td>Brother or sister</td>
</tr>
<tr>
<td>(d)</td>
<td>Grandparent or grandchild</td>
</tr>
<tr>
<td>(e)</td>
<td>Child of a brother or sister</td>
</tr>
<tr>
<td>(f)</td>
<td>Stepfather or stepmother</td>
</tr>
<tr>
<td>(g)</td>
<td>Half brother or half sister</td>
</tr>
<tr>
<td>(h)</td>
<td>Friend of long standing.</td>
</tr>
</tbody>
</table>

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.

**Adults lacking capacity**

19. 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, taking into account the conditions and principles applying to subjects 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 ethical 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,
20. For further guidance on approval for research involving adults lacking capacity, refer to Section 12 of SOPs.

Further guidance on consent

21. 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.

22. 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

23. 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.

24. 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 25-26).

25. 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 26).

Exemption for ethically approved research

26. 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 ethical approval was given before the commencement of the HT Act)

• For the purpose of a specific research project for which ethical approval is pending (i.e. an application for ethical approval has been submitted but a final opinion has not yet been given).

27. Ethical 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).

28. 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

29. 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.

30. Diagnostic archives may make voluntary applications for ethical review as a research tissue bank under Section 11 of SOPs.


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 ([http://www.hta.gov.uk/licensingandinspections.cfm](http://www.hta.gov.uk/licensingandinspections.cfm)). A summary is available in the MRC Data and Tissues Toolkit published at [http://www.dt-toolkit.ac.uk/home.cfm](http://www.dt-toolkit.ac.uk/home.cfm).

### 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.


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 2.6 below).

41. Under Scottish law a child is defined as a person aged under 16.

Ethical 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) Regulations 2004, 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).

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ANNEX J: The Gene Therapy Advisory Committee

Remit of GTAC

1. The Gene Therapy Advisory Committee (GTAC) is the national Research Ethics Committee for ethical review of research involving advanced therapy medicinal products in the UK. GTAC is part of the National Research Ethics Service.

Advanced therapy medicinal products (ATMPs)

2. Advanced therapy medicinal products (ATMPs) are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or as part of active substances.


4. ATMPs include the following types of product:
   - Gene therapy medicinal products
   - Somatic cell therapy medicinal products
   - Tissue engineered product

5. Trials involving all of these products are reviewed by GTAC.

Gene therapy

6. Under the Clinical Trials Regulations, all clinical trials of investigational medicinal products for gene therapy must be submitted to GTAC. (For procedures for transfer of applications to other REC, see paragraphs 26-38 below.)

7. Gene therapy medicinal products are defined in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC) as follows:

   “… [a] gene therapy medicinal product means a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.”

8. The definition of gene therapy medicinal products specifically excludes products which are vaccines against infectious diseases.

9. In addition to CTIMPs, it is recommended that researchers undertaking other non-CTIMP studies in gene therapy also apply to GTAC so that it can maintain a comprehensive oversight of this field of research. This might apply, for example, to non-interventional follow-up studies involving patients treated with gene therapy.
Somatic cell therapy

10. A somatic cell therapy medicinal product is defined in Part IV of Annex 1 to Directive 2001/83/EC as follows:

   “somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g. adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g. micro-capsules, intrinsic matrix scaffolds, bio-degradable or not)."

- Somatic cell therapy medicinal products include:
- Cells manipulated to modify their immunological, metabolic or other functional properties in qualitative or quantitative aspects
- Cells sorted, selected and manipulated and subsequently undergoing a manufacturing process in order to obtain the finished medicinal product
- Cells manipulated and combined with non-cellular components (e.g. biological or inert matrixes or medical devices) and exerting the principle intended action in the finished product
- Autologous cell derivatives expressed in vitro under specific culture conditions
- Cells genetically modified or otherwise manipulated to express previously unexpressed homologous or non-homologous functional properties.

The whole manufacturing process from the collection of the cells from the patient (autologous situation) up to the re-injection to the patient shall be considered as one single intervention.

Tissue engineered product

11. A tissue engineered product means a product that:

- contains or consists of engineered cells or tissues, and
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

12. A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Do tissue engineered products have to contain living cells?

Yes. Products containing or consisting exclusively of non-viable human or animal cells, and/or tissues which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from the definition.
Cells or tissues considered to be engineered

13. Cells or tissues are considered to be ‘engineered’ if they fulfil at least one of the following conditions:
   - the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor; or
   - the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.
   - (Substantial manipulation does not include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation or vitrification.)

Combined ATMPs

14. A ‘combined advanced therapy medicinal product’ means an ATMP that fulfils the following conditions:
   - it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and
   - its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.’

Stem cell therapy

15. In addition to ATMPs, GTAC is the national flagged REC for trials of novel stem cell therapy derived from stem cell lines.

Types of stem cell therapy reviewed by GTAC

16. A stem cell line is defined as a permanently established culture of unspecialised cells derived from a single parental cell, or group of parental cells, that can (i) proliferate in vitro for a prolonged period when given appropriate nutrition and space and (ii) be made to differentiate in culture into more specialised types when given appropriate chemical or molecular cues.

17. The remit of GTAC includes cell therapies derived from:
   - genetically modified cells;
   - embryonic stem cell lines;
   - multipotent stem cell lines;
   - mesenchymal stem cell lines;
foetal stem cell lines; and
induced pluripotent stem (iPS) cell lines.

18. Other types of research study involving well established autologous stem cell therapies not involving genetically modified or manipulated cells (for example, bone marrow transplantation) may continue to be reviewed by any appropriate REC.

Background - what are stem cells?

19. Researchers have been able to grow certain types of stem cells apparently indefinitely in the laboratory. Called a stem cell line, these cells have two very important properties. Firstly, they can self-renew or form ‘carbon copies’ of themselves. Secondly, they can be made to differentiate, or convert, into any one of the different types of specialised cell in the human body. Stem cells which can differentiate into any type of cell in the body are referred to as pluripotent. For example, stem cell lines derived from the early embryo, or embryonic stem cells, are pluripotent.

20. Some of our fully developed tissues also possess stem cells, known as adult stem cells. These stem cells are different from embryonic stem cells because they cannot form any type of cell in the body, that is, they are not pluripotent. Adult stem cells can, however, effectively replace a small number of cell types within their tissue of origin.

21. A very recent breakthrough has shown that normal adult body cells can be ‘reprogrammed’, or switched back, into stem cells that appear to show all the properties of embryonic stem cells. This is done by ‘re-programming’ the nucleus of adult body cells using genetic modification so that the cells revert back to their earliest developmental stage in the embryo.

What is stem cell therapy?

22. Perhaps the most successful medical exploitation of stem cells to date has been the use of bone marrow transplantation as therapy for a variety of cancers of the blood and immune systems. Researchers are now hoping to exploit other forms of adult stem cell to treat diseased or damaged tissues of patients.

23. Given their unrestricted potential to form any kind of cell in the body, scientists have more recently begun to research the possibility of using embryonic stem cell lines to generate replacement cells for a range of diseases where there are unmet medical needs. Because the embryonic stem cell lines can be grown in large amounts, it should be possible to generate sufficient quantities of cells to replace damaged or diseased tissue in patients. This type of approach is known as stem cell therapy or regenerative medicine. Induced pluripotent stem (iPS) cell lines may also hold the same promise as embryonic stem cells in contributing to the development of novel medical treatments and cell therapy.

24. A UK Stem Cell Toolkit has been developed by UK regulators as a reference tool for those who wish to develop a programme of human stem cell research and manufacture, ultimately leading to clinical application (see http://www.sc-toolkit.ac.uk/home.cfm).
Further advice

25. Further advice on the types of study it is appropriate for GTAC to review may be sought from the GTAC Co-ordinator.

Procedures for transfer of low risk gene therapy applications to other RECs

26. Under the Clinical Trials Regulations, all applications for ethical review of clinical trials of investigational medicinal products for gene therapy must be made to GTAC. However, the Regulations make provision for GTAC to notify the UKECA that its opinion is not required on an application and for the UKECA to direct that the application should be considered by another recognised committee. The functions of UKECA in relation to such transfers are carried out on its behalf by NRES.

27. NRES has flagged a small group of recognised RECs to receive gene therapy applications on transfer from GTAC.

28. This Annex sets out the procedures to be followed by GTAC and flagged RECs when arranging transfers.

Recommendations for transfer

29. GTAC has developed a decision tree to indicate the types of low risk gene therapy trial that will be considered for transfer (see Figure 1).

30. Recommendations to arrange transfer will be made by the Chair of GTAC (or vice-chair or alternate vice-chair) on advice from the GTAC Co-ordinator.

Arranging the transfer

31. The GTAC Co-ordinator will notify the applicant that it plans to transfer the application. The applicant may indicate a preference for a particular flagged REC. The GTAC Co-ordinator will then contact a flagged REC directly by phone or email to advise that it wishes to transfer an application. If an agenda slot is available at the next meeting, the REC Co-ordinator should accept the transfer, book the application and allocate a REC reference number. If the agenda for the next meeting is full, the GTAC Co-ordinator should be advised to contact other flagged RECs. In case of any difficulty identifying a suitable agenda slot, the GTAC Co-ordinator should be advised to contact the REC operational manager for further advice.

32. Once a booking has been made, the GTAC Co-ordinator will notify the applicant and make arrangements to transfer the application to the relevant REC (“the second REC”) within RED.

Validating the application

33. Responsibility for validating the application lies with the Co-ordinator of the second REC. However, the GTAC Co-ordinator will undertake a preliminary check of the application and will notify the applicant and the Co-ordinator of the second REC of
any documents it has identified as missing, in order to minimise any delay in providing a complete application.

34. The validation date is the date of receipt of a complete application by a recognised committee. The Co-ordinator of the second REC should confer with the GTAC Co-ordinator to determine the validation date. *This will normally be the date of receipt by GTAC*. If the GTAC submission was incomplete, the validation date will be the date on which the last part of the required documentation is received by the second REC.

**Ethical review**

35. The usual SOPs apply to the review of an application on transfer, with the following exceptions.

36. Under the Regulations, the time limit for giving an opinion on a gene therapy application is 90 days rather than the usual 60 days. This time limit applies to applications transferred from GTAC in the same way as any other application reviewed by GTAC. The clock on RED will therefore be adjusted to allow the REC up to 90 calendar days to give an opinion from the validation date.

37. The second REC has the discretion to seek the advice of GTAC on the application if required. If so, the Co-ordinator should contact the GTAC Co-ordinator by phone or email to discuss the advice required and the options for providing it. These include:

- Written advice from the GTAC Co-ordinator or from a member of GTAC, acting as a referee
- Co-opting a GTAC member to attend either the full Committee meeting or a sub-committee meeting.

38. Copies of all letters sent to the applicant by the second REC should be copied to the GTAC Co-ordinator for information. Following issue of a favourable opinion, any further correspondence with the Chief Investigator or sponsor (e.g. on substantial amendments or safety reports) should also be copied to the GTAC Co-ordinator. The advice of GTAC may be sought during the trial if necessary.
Figure 1: Decision tree to guide to researchers as to the types of trial that may be considered for transfer.

1. Is this a phase III trial? YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

2. Is the GT-IMP subject to MHRA’s provisions for first-in-man (FIM) trials? YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

   Category 3 trial: GTAC is likely to recommend transfer unless the patient population is significantly different than with previous trials.

3. Is the study conducted in immunocompromised individuals? YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

   Category 2 trial: Transfer may be considered on a case-by-case basis at the request of the applicant.

   Category 1 trial: GTAC will wish to review the trial (no transfer).

4. Is the GT-IMP a plasmid (or series of plasmids)? YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

5. Is the GT-IMP:
   - an integrating virus (lenti or retrovirus) or
   - a partially integrating virus (such as AAV) or
   - a replicating virus or
   - a novel virus (e.g. rare human adenovirus serotype, pseudotype or animal virus) or
   - used for ex vivo transduction of cells (stem cells or T-cells) with the modified cells re-introduced into the patient or
   YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

6. Is the transgene:
   - a growth factor or
   - cell cycle regulating protein or
   - an anti-apoptotic or
   - coding for a protein that may result in production of auto-antibodies
   YES
   NO
   Category 1 trial: GTAC will wish to review the trial (no transfer).

7. Has the product been approved previously by GTAC in the same disease application and by the same method of administration? YES
   NO
   Category 3 trial: GTAC is likely to recommend transfer.

8. Is this a phase I trial? YES
   NO
   Category 2 trial: Transfer will be considered on a case-by-case basis at the request of the applicant.

9. Is this a cancer-vaccine approach or vaccine for infectious disease where the vaccine is administered locally not systematically? YES
   NO
   Category 3 trial: GTAC is likely to recommend transfer if the vector is well-characterised.
ANNEX K: The Social Care Research Ethics Committee

1. The Social Care REC reviews adult social care research and some applications for social sciences research (see paragraph 6 below). It is part of the National Research Ethics Service (NRES), and its membership, expertise and procedures have been developed to reflect the social care context. The Appointing Authority is the Social Care Institute for Excellence (SCIE). Committee members, recruited through open advertisement, include researchers, ethicists, providers and users of social care.

2. The Social Care REC reviews applications involving the social care sector (e.g. in local authority, private and voluntary care settings) that would not otherwise have access to ethical review, or which cross sector boundaries. It generally expects to review the following types of study:

2.1 Social care studies funded by Department of Health:
   - Research commissioned directly through the Policy Research Programme
   - Information Centre (IC) studies (i.e. those to be designed by IC for implementation by Councils with Adult Social Services Responsibilities, who do not then individually need to seek additional review)
   - Studies commissioned by or through National Institute for Health Research (NIHR) School for Social Care Research
   - Social care studies funded (in rare cases) through NIHR.

2.2 Social care research that involves adults lacking capacity in England and Wales and requires approval under the Mental Capacity Act 2005. The Social Care REC is recognised by the Secretary of State and the Welsh Ministers as an Appropriate Body for this purpose.

2.3 Social care research involving sites in England and another United Kingdom country.

2.4 ‘Own account’ research undertaken by Councils with social service responsibilities, where the Chief Investigator and/or the sponsor consider there are significant ethical issues.

2.5 Studies where investigators do not have access to other review systems. This could include service user-led research.

2.6 Studies taking place in NHS settings with NHS patients or staff where the approach to data collection uses social science or qualitative methods, provided that the research does not involve any clinical interventions or changes to clinical care. A study collecting patients’ views of care and treatment through structured questionnaires or qualitative interviews would be an example of this type of study. Studies taking place in joint health and social care settings (such as a community mental health team venue) may also be reviewed within this category.
2.7 Intergenerational studies in social care, where both adults and children, or families, are research participants.

3. Researchers unsure about their options for seeking ethical review should seek guidance from the Social Care REC Co-ordinator (see paragraph 6 below).

4. Opinions given by the Social Care REC on studies taking place within the NHS (within 2.6 or 2.8 above) have the same status as any other REC within the UK Health Departments’ Research Ethics Service. Such studies do not require separate review by a REC established within the NHS.

5. All applications to the Social Care REC should be prepared using IRAS.

6. **Bookings are made directly to the Co-ordinator at SCIE email** screc@scie.org.uk. **Visit** www.screc.org.uk.
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