Standard Operating Procedures
for
Health Research Ethics Committees
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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Introduction

Purpose and scope
1. This standard operating procedures (SOP) is designed to guide the operation of health research ethics committees in accordance with the tenets of the Nigerian National Code for Health Research Ethics (NCHRE).
2. The NCHRE was issued by the National Health Research Ethics Committee (NHREC) in accordance with Nigerian law and policy guidelines and came into effect on 1 January 2007.
3. The policy of the Federal Ministry of Health is that the National Code for Health Research Ethics should apply to the review of research by Health Research Ethics Committees (HREC) in all research involving human participants anywhere in Nigeria.
4. The NHREC co-ordinates the development of guidelines and SOPs for HREC, including systems to enable relevant committees to comply with the Clinical Trials Regulations issued by National Agency for Food and Drug Administration and Control (NAFDAC).
5. Adoption of this SOP is optional. This SOP applies to all HREC that review research in Nigeria.
6. Recognised HREC can adopt this SOP in its entirety or develop their own, to the degree that this is in consistent with the NCHRE.
7. Any recognised HREC proposing to develop its own SOP should notify the Secretary of the NHREC so that arrangements can be made for these to be reviewed by NHREC for consistency.
8. For purposes of clarity, the NCHRE is the guidance document for all health research in Nigeria and where any other guideline or document conflicts with the National Code, the National Code shall prevail.

Implementation
1. This version of the HREC SOP is due to come into effect on 1 January 2008. (The implementation date will be confirmed on the NHREC website.)
2. The system of categorization of HREC being implemented by NHREC for the accreditation of HREC will take application of this SOP into consideration.
3. HREC may develop additional local operating procedures to deal with local matters not addressed in this SOP or where discretion is permitted.
Terminology
A guide to the terminology used in this SOP is set out below. The following should be noted in particular:

- Responsibilities assigned in this SOP to the NHREC may be delegated to any member of NHREC by the Chairman of NHREC.
- All references to “the Chair” of the REC should be interpreted as referring also to his designee or someone acting in place of the Chair
- The “main HREC” means the HREC undertaking the ethical review of an application or, in the case of research that is underway, the HREC that is providing oversight of the research. In the case of research studies with ethical approvals from more than one HREC, one of the HREC should be appointed as main REC to review amendments.

Further information
HREC requiring further information or advice should contact the NHREC by e-mail at
National Health Research Ethics Committee
Federal Ministry of Health
Federal Secretariat Complex
Shehu Shagari Way
P.M.B. 083, Garki – Abuja,
Abuja, Nigeria
E-mail: secretary@nhrec.net, deskofficer@nhrec.net
Website: http://www.nhrec.net
Glossary

Amendment
A change made to the research protocol submitted and for which HREC approval was approved or any of the supporting documentation after the study has started. A study is normally considered to have started when any of the components of the research protocol is carried out.

Appointing authority
A body responsible under National Code for Health Research Ethics for the establishment and support of a HREC.

Appeal
Following the issue of an order to terminate research, application may be made to the NHREC.

Approval conditions
Conditions to be observed by the applicant in the conduct of the research. Approval conditions are issued by the HREC with 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.)

Authorised HREC
A HREC established under NCHRE and registered by NHREC

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.

Chair
The member of a HREC appointed to be Chair by the appointing authority. Where the Chair is unavailable, his/her duties may be performed by the vice-Chair.

Principal Investigator (PI)
The investigator with overall responsibility for the research. In a multi-site study, the PI has co-ordinating responsibility for
research at all sites. All applications for ethical review should be submitted by the PI. In international collaborative research, with a principal investigator abroad and there are multiple sites in Nigeria, where there are less than 3 sites and the PI chooses to obtain ethics review from the HREC of each of these institutions, then the lead investigator in each institution is a principal investigator. On the other hand where the overall international principal investigator chooses central review by the NHREC, then one local investigator should be designated as the Nigerian Principal Investigator.

CIOMS
Council for International Organizations of Medical Sciences

Clinical Trials Guidelines
The guidelines issued by NAFDAC for the conduct of clinical trials

Employing organisation
An organisation employing the Principal Investigator, and possibly other investigators or research collaborators.

IMP
Investigational medicinal product.

Lead site
In the case of a multi-site study, the site the Principal Investigator has primary academic, research or clinical appointment as the case may be.

Collaborating Investigator
A person undertaking certain parts of a research procedure other than the principal investigator.

HREC
Local Health Research Ethics Committee.

Main HREC
In the case of multi-site studies, the HREC undertaking the ethical review of the application.

“No local investigator” study
A term used to describe studies with non-resident Principal Investigator at research sites.
Operations Director

The senior manager at COREC responsible for day-to-day operational management of the REC system through the ORECs. Responsibilities of the Operations Director under the SOPs may be delegated to another member of staff at COREC.

OREC

Office for Research Ethics Committees, a network of COREC offices responsible for professional oversight and support of all RECs in the UK.

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.)

Principal Investigator (PI)

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

Provisional opinion

A decision reached by a REC on an application, subject to the receipt of further information or clarification from the applicant. The 60 day time period is suspended until the information is received.

REC

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

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 to be undertaken anywhere in the UK.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referee</td>
<td>A person or body who gives expert advice to a REC on an application or any related matter.</td>
</tr>
<tr>
<td>Research site</td>
<td>The organisation or unit responsible for conducting the research at a particular locality (see paragraphs 4.10-4.18).</td>
</tr>
<tr>
<td>Revision of application</td>
<td>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.</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event (see statutory definition on page 26).</td>
</tr>
<tr>
<td>Second REC</td>
<td>The REC that reviews an application on appeal following the issue of an unfavourable opinion by the “first REC”.</td>
</tr>
<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 an appropriate LREC or another body appointed by the OREC Manager.</td>
</tr>
<tr>
<td>60 day clock</td>
<td>The period of 60 calendar days allowed by the EU Directive and the Clinical Trials Regulations for the issue of an ethical opinion on an application. The clock starts on receipt of a valid application and may stop once while awaiting a complete response from the applicant to one written request from the REC for further information or clarification.</td>
</tr>
<tr>
<td>SSA</td>
<td>Site-specific assessment, an assessment of the suitability of the investigator, site and facilities made for any study with a Principal Investigator at each research site. The application for SSA should be made by the Principal Investigator using Part C</td>
</tr>
</tbody>
</table>
of the application form. In the case of a multi-site study, the outcome of the SSA should be notified to the main REC within 25 days.

SSA exemption

Research sites not requiring site-specific assessment are described as “SSA-exempt”. The main REC is responsible for deciding on SSA exemption, taking into account the guidance in paragraphs 4.20-4.32. The main REC may issue the ethical opinion for all sites in a SSA-exempt study without the need for SSA by LRECs at each site.

SOPs

The Standard Operating Procedures issued by COREC.

Sponsor

See statutory definition on page 27.

SSAR

Suspected Serious Adverse Reaction (see statutory definition on page 28).

Substantial amendment

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 always requires the issue of a favourable opinion from the main REC.

SUSAR

Suspected Unexpected Serious Adverse Reaction (see statutory definition on page 28).

35 day clock

The period of 35 days allowed by the Directive and the Clinical Trials Regulations for the issue of an ethical opinion on a substantial amendment. There is no provision for the clock to stop while awaiting any further information.

Transfer

The transfer of an application by the receiving REC to another REC for review.
UKECA  United Kingdom Ethics Committee Authority.

Validation  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.

Validation date  The date on which a valid application is received by a REC (see paragraph 1.45).
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: Any investigator at a site in a CTIMP must be one of the above. See under “health care 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 care 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.

**Health care professional**

A health care 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</td>
</tr>
</tbody>
</table>
and 1954, or Articles 6 and 9 of the Pharmacy (Northern Ireland) Order 1976

<table>
<thead>
<tr>
<th>Profession</th>
<th>Definition or Source</th>
</tr>
</thead>
<tbody>
<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 health care 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, dietitians, medical laboratory technicians, occupational therapists, orthoptists, paramedics, physiotherapists, prosthethists 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:

1. used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation
2. used for an indication not included in the summary of product characteristics under the authorisation for that product
3. 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 group of 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.
Section 1: New applications for ethical review

Summary

New applications must be submitted by the Chief Investigator (CI) on the national REC application form. Only one application for ethical review should be made for any research study in the UK. The ethical opinion should be given within a maximum of 60 days.

Applications are generally divided into two types, clinical trials of investigational medicinal products (CTIMPs), and all other research. The review of CTIMPs is governed by the EU Clinical Trials Directive, incorporated into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004.

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

The Clinical Trials Regulations require CTIMPs to be reviewed by RECs that are legally “recognised” by the United Kingdom Ethics Committee Authority (UKECA). There are three types of recognised committee:

Type 1: Phase 1 clinical trials in healthy volunteers taking place anywhere in the UK
Type 2: Clinical trials in patients taking place in one NHS domain only
Type 3: Clinical trials in patients taking place anywhere in the UK.

NHS RECs that are not recognised by UKECA are referred to as “authorised” RECs and can review any NHS research other than CTIMPs.

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 COREC Central Allocation System (CAS) is a telephone booking service, which allocates certain types of application to recognised RECs throughout the UK. All CTIMPs in patients, and research involving sites in more than one NHS domain, are allocated through CAS. Phase 1 CTIMPs in healthy volunteers are booked directly with a Type 1 recognised committee. Other applications are booked directly by phone with a Local Research Ethics Committee in the NHS domain where the research is to be conducted. Applications are given a REC reference number and booked at a meeting for review.

Applications and supporting documentation must usually be submitted within 4 days of booking the application. The application form must be submitted both electronically and on paper with signatures. The REC Co-ordinator then has 5 working days to validate the application and respond to the applicant. Section 1 defines the “validation date” and the criteria for validating an 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.

Finally, this section gives guidance on dealing with applications submitted retrospectively or which are outside the remit of a NHS REC.
Section 1 New applications for ethical 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 be professionally based in the United Kingdom. For international studies with a co-ordinating investigator outside the UK, a health professional based in the UK should be nominated as the Chief Investigator responsible for the conduct of the research 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. In the case of multi-site 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.

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.

1.4 All new applications for ethical review to a Research Ethics Committee (REC) in the UK should be submitted on the electronic standard NHS REC application form, as published on the website of the Central Office for Research Ethics Committees (http://www.corec.org.uk/). The standard application form may be revised from time to time by COREC. (See paragraph 1.8 for additional documentation required for a valid application.)

1.5 Applications should be booked for review prior to submission (see paragraph 1.21-1.33 for detailed booking procedures). Bookings should be made either direct with a Local Research Ethics Committee (LREC) in the domain in which the research is to be conducted, or through the COREC Central Allocation System (CAS), depending on the type of application.
Allocation of new applications

1.6 With certain exceptions, which are set out in paragraphs 1.34-1.38, new applications for ethical review should be booked and allocated for review as in Tables A and B. Circumstances in which applications may be transferred to another REC, and the procedures to be followed, are described in paragraphs 1.61-1.75.

A. 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</td>
<td>Direct with Committee</td>
<td>Type 1 recognised ethics committee (either NHS REC or private committee).</td>
</tr>
<tr>
<td>Single domain trial in patients</td>
<td>Via CAS</td>
<td>Type 2 or Type 3 recognised NHS REC.</td>
</tr>
<tr>
<td>Multi-domain trial in patients</td>
<td>Via CAS</td>
<td>Type 3 recognised NHS REC.</td>
</tr>
</tbody>
</table>

B. All other research

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Booking procedure</th>
<th>Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single domain study</td>
<td>Direct with Committee (or exceptionally via CAS if study is likely to be extended beyond the domain)</td>
<td>Normally to NHS LREC within the domain.</td>
</tr>
<tr>
<td>Multi-domain study</td>
<td>Via CAS</td>
<td>Normally to Type 2 or Type 3 recognised NHS REC, but CAS may allocate to any NHS REC if appropriate.</td>
</tr>
</tbody>
</table>
Research sites and domains

1.7 The research domain(s) is the area(s) of the UK in which the research sites are located and in which the research is actually conducted. It is not relevant where the research participants are resident, or which Primary Care Trust is responsible for the participants’ primary care. The only domains where the research is conducted are those in which participant-related research procedures specified in the protocol - including recruitment and informed consent - are carried out. Referral of a patient (possibly from another domain) for assessment and possible recruitment is not part of the conduct of the trial. The following are not considered to be research sites:

- Clinicians or clinical units making referrals to the research team
- Research units undertaking support functions, e.g. project management, site monitoring, data analysis, report writing.

1.8 A “domain” is defined as follows:

- In England, the area covered by a NHS Strategic Health Authority
- In Wales, the area covered by one of the regional offices of the NHS Wales Department
- In Scotland, the area covered by a NHS Health Board
- The whole of Northern Ireland under the aegis of Health and Personal Social Services.

1.9 Guidance on the definition of a “research site” is set out in paragraphs 4.10-4.18.

1.10 Where the Chief Investigator plans eventually to conduct a study at sites in two or more domains, it should be allocated for review as a multi-domain study, even where research sites have so far been identified in one domain only.
1.11 In rare cases, a study may be taking place at a single research site spanning the boundaries of two domains. If the study is a CTIMP, it should be allocated by CAS to a Type 3 REC. If it is not a CTIMP, the application may be made direct to the relevant LREC.

Allocation of CTIMPs to recognised ethics committees

1.12 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.

1.13 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 in healthy volunteers taking place at any site in the United Kingdom.

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 (see paragraph 1.8).

Type 3 Committees recognised to review CTIMPs in patients (whether Phase 1 or later phase) taking place at any site in the UK.

Non-interventional trials

1.14 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.

1.15 The MHRA has published guidance on the interpretation of the statutory definition of CTIMP and non-interventional trials (see algorithm at Annex F). If a REC receives an application that has incorrectly been declared to be a non-CTIMP, the Co-ordinator should treat it as invalid (see paragraph 1.60). The application form will not contain a EudraCT number or all the supporting information required about a CTIMP, and it
may also have been received by a REC without appropriate recognition. The application should be revised and re-booked as a CTIMP through CAS. 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. 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).

Studies involving healthy volunteers

1.16 Any clinical trial of an investigational medicinal product in which the participants are healthy volunteers should be regarded as a Phase 1 CTIMP (see definition in the Glossary) and submitted direct to a Type 1 recognised REC. There are, however, some research studies involving healthy volunteers that are not clinical trials and/or do not involve investigational medicinal products. Such studies should be allocated in accordance with the normal procedures for non-CTIMPs.

Phase 1 trials in patients

1.17 A phase 1 CTIMP in patients may legally be reviewed by any Type 2 or Type 3 recognised REC. However, where a REC does not have the expertise to review such trials it may be agreed that it will not be allocated any Phase 1 trials.

Allocation of non-CTIMPs

1.18 Recognition of ethics committees by UKECA legally applies only to the review of CTIMPs. In legal terms, applications relating to non-CTIMPs may be reviewed by any authorised REC. However, for operational purposes CAS will use the recognition criteria to determine the allocation of multi-domain non-CTIMPs. In practice such studies will normally be allocated to Type 3 RECs, although where special circumstances apply they may be allocated to a Type 2 REC or exceptionally to an authorised REC at the discretion of the Operations Director. Such circumstances might include the following:

- No suitable agenda slot is available at a Type 3 REC
- Another Committee has reviewed a previous, closely related study
Another Committee has special expertise in the research field
The study is to be conducted at a small number of sites spanning a domain boundary.

1.19 Single-domain non-CTIMPs should normally be booked direct with the appropriate LREC. (Exceptionally the applicant may opt to book through CAS if the study is likely to be extended beyond the domain.) The Chief Investigator should normally approach first the LREC for the area in which the research is to be conducted. If an agenda slot is not available, the applicant may approach any other LREC within the domain. Where no LREC is established within the domain, or no agenda slot is available within the domain, the application may be submitted to a LREC in another domain within the OREC area, or exceptionally in another OREC area.

1.20 In the case of multi-site research that is to be conducted within a single domain, the applicant should normally approach first the LREC for the lead site. If an agenda slot is not available, the applicant may approach a LREC for one of the other trial sites or any other LREC within the domain.

Procedures for booking and submitting applications

Telephone bookings

1.21 An applicant intending to submit a new application should first contact either the LREC Office or CAS, as appropriate, in order to:

- Seek advice on the correct allocation of the application
- Book an agenda slot at the next meeting of the appropriate REC
- Obtain a REC reference number for the application, which should be entered on the application form prior to submission
- Check the closing date for submission of the application.

1.22 When giving advice, the LREC Co-ordinator or CAS Co-ordinator may use model booking checklists issued by COREC. It is especially important to check the correct allocation, taking into account the type of study and the number of domains in which the applicant plans to conduct it. It may also be useful to make a preliminary check of the validity of the application.
1.23 Co-ordinators should check that the applicant is ready to submit the application before accepting the booking, and give advice on the procedures for submission. Once the booking has been accepted, confirmation of the booking should be sent to the applicant by e-mail, together with the REC reference number and the closing date for receipt of the application. In the case of bookings made by CAS, the Co-ordinator of the REC to which the application has been allocated should also be notified by e-mail.

 Submission of application documentation

1.24 Applications through CAS should be submitted to the REC to which the application has been allocated within the next 4 working days in order to retain the booking. In the case of local applications, LREC Co-ordinators may require that the application should be submitted within 4 working days or at any specified time until the closing date for the next meeting.

1.25 When booking agenda slots well in advance of the closing date for the next meeting, LREC Co-ordinators should consider the need to give an ethical opinion within 60 days of receipt of a valid application. Applicants who intend to submit an application to a LREC more than two weeks ahead of the closing date for the next meeting should normally be advised to contact another LREC within the domain that is able to offer an earlier meeting slot. Bookings may be accepted more than two weeks ahead of the closing date provided that the application itself is received within two weeks of the closing date. If the application is received earlier than this, the Co-ordinator should normally arrange for it to be transferred (see paragraphs 1.62-1.63).

1.26 The application form should be submitted electronically to the appropriate REC office by the date specified by CAS or the LREC Co-ordinator. In addition, one paper copy of the form, with all relevant signatures in ink, should normally also be sent to the REC office by the specified date.  

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1 In the case of a CTIMP, the Clinical Trials Regulations allow for the Chief Investigator to sign the application by means of an electronic signature (see Glossary). Where an applicant for a CTIMP proposes to use this facility instead of submitting a paper copy with ink signature, the Co-ordinator should consult the OREC Manager for advice. Electronic signature should not be permitted in the case of non-CTIMPs.
1.27 The applicant should also submit, by the specified date, the completed application checklist and all supporting documents as indicated on the checklist.

1.28 Additional photocopying of application documentation for REC members is the responsibility of the REC office.

*Bookings with CAS – taking account of the applicant’s preferences*

1.29 Applicants making a telephone booking with CAS should be offered the first available meeting slot at an appropriate REC. If the applicant agrees, the application should be assigned to this meeting.

1.30 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). 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 may opt to wait for the following meeting, or other options may be discussed.

1.31 Once a suitable agenda slot has been agreed with the applicant, CAS should book the application, and advise both the applicant and the REC of the REC reference number.

1.32 If the applicant declines the next available agenda slot in order to secure a slot at their preferred REC, the validation date (see paragraph 1.45) will be the closing date of the meeting to which the application is assigned.

*OREC allocation systems*

1.33 OREC Managers have the discretion to introduce systems for central allocation of applications to LRECs within their areas of responsibility, subject to the approval of the Operations Director at COREC.
Special allocations

Applications involving prisoners

1.34 Except in Scotland, any application in which the research participants include prisoners\(^1\) (as declared on the application form at A24) should be allocated through CAS to the RECs designated by COREC to review such research. In Scotland, the application may be made direct to the relevant LREC if the research is within a single domain; if it is multi-domain, it should be allocated through CAS.

Applications involving adults with incapacity in Scotland

1.35 Any application in which the research participants include adults in Scotland who are physically or mentally unable to consent for themselves (as declared on the application form at A24) should be allocated through CAS.

1.36 If the application is a CTIMP, and the research is to be conducted at one or more sites in Scotland, and the Chief Investigator is professionally based in Scotland, it should be allocated by CAS to “the Ethics Committee” constituted by Scottish Ministers under the Adults with Incapacity (Scotland) Act 2000. This committee is currently the MREC for Scotland Committee A. If the Chief Investigator is professionally based outside Scotland, the application may be allocated to any Type 3 recognised REC. 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 applies.

1.37 If the application relates to a research study other than a CTIMP, and the research is to be conducted at one or more sites in Scotland, there is a legal requirement under the Adults with Incapacity (Scotland) Act 2000 for the research to be approved by “the Ethics Committee” constituted by Scottish Ministers under the Act. The application should therefore be allocated by CAS to the MREC for Scotland Committee A. This

\(^{1}\) A prisoner is defined for this purpose as any inmate of the prison services of England and Wales, Scotland or Northern Ireland. This does 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.
applies even where the Chief Investigator is professionally based outside Scotland. The provisions of the 2000 Act apply to the ethical review of such research in relation to participants in Scotland.

1.38 For guidance on site-specific assessments and the addition of further sites involving adults with incapacity in Scotland, see paragraphs 4.88 and paragraph 5.68 respectively.

Entry of applications on the Research Ethics Database (RED)

1.39 Applications should be entered on the Research Ethics Database (RED) at the time of the telephone booking, either by the CAS Co-ordinator or the LREC Co-ordinator, as appropriate.

Applications submitted without prior booking

1.40 If an application has been submitted without prior booking by the applicant, it will not have a REC reference number or an agreed agenda slot, and may also have been submitted to a REC that is unable to review it.

1.41 In such cases, the Co-ordinator should:

- Enter the application on RED, whether it is to be retained or transferred, and generate a REC reference number.

- Consider whether the application can be accepted for review at the next meeting of the REC. If so, the application should be booked.

- Inform CAS of any such booking by a MREC, or by a recognised LREC if the application relates to a CTIMP or multi-domain study.

- If the application cannot be accepted for review, arrange transfer in accordance with the procedures in paragraph 1.61-1.75.
Reserved agenda slots at recognised RECs

1.42 Recognised LRECs will receive bookings both through CAS and direct from applicants. A specified number of agenda slots at each meeting should be reserved for CAS allocation by agreement of the OREC Manager and the Chair of the LREC. All bookings made by CAS should be notified to the LREC Co-ordinator. If a reserved slot remains unfilled one week prior to the LREC’s closing date for submission of applications, it may be re-allocated by the LREC Co-ordinator to a local applicant; if so CAS should be notified.

1.43 MREC agenda will be filled entirely by allocation from CAS. The number of agenda slots at MRECs should be agreed between the OREC Manager, the Chair and the Operations Director at COREC.

Validation of applications

The validation date

1.44 The period of 60 days, within which an ethical opinion must be given, begins when a valid application is received by any REC.

1.45 The relevant date (“the validation date”) is the working day on which the complete application, including all relevant signatures and all supporting documents, is delivered to the address of the REC, either in electronic or paper format. This applies whether or not the Co-ordinator or another member of the REC office staff is present to receive the application. Where packages are not date stamped on receipt, the date of receipt should be presumed to be the working day after the day of posting (1st class post) or the third working day after posting (2nd class post).

Decision on validation

1.46 It is normally the responsibility of the receiving REC 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. Where an application is
transferred to another REC, responsibility for validation passes to the REC to which the application is transferred (see paragraphs 1.72-1.75).

1.47 The decision whether or not an application is valid should normally be made by the REC Co-ordinator. The agreement of the Chair is not required.

Validation criteria

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

(a) The applicant’s checklist has been completed and submitted.

(b) All documents listed in the checklist have been submitted. (The checklists indicate which documents are mandatory for all applications.)

(c) Part A of the standard application form has been submitted, together with the applicant’s declaration in Part B and other sections of Part B where applicable. (In some cases Part C should also be submitted initially – see paragraph 1.50). The form should be submitted both electronically and on paper (unless it contains electronic signatures\(^1\)). The form must be in typescript.

(d) All relevant sections and questions in the application form have been completed (see paragraph 1.51), the text is in English and the print is clearly legible.

(e) The application form has been signed by the Chief Investigator (all applications) and, where applicable, by the Radiation Protection Adviser/Medical Physics Expert and IRMER Practitioner (research involving the use of radiation); by the educational supervisor (applications submitted by students); by the Tissue Bank Manager (research involving use of existing stored samples); and by the prison governor and health professional at each participating establishment (research involving prisoners).

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\(^1\) See footnote to paragraph 1.26.
(f) Short curriculum vitae (maximum two pages) have been submitted for the Chief Investigator and, in the case of student applications, for the educational supervisor.

(g) 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.

(h) 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.)

(i) The sponsor (or one of the co-sponsors if applicable) has been named on the application form (at A59).

(j) Evidence has been provided, in the case of trials with a sponsor(s) outside the NHS, that the sponsor(s) and Chief Investigator have insurance or indemnity to cover any potential liability arising from the research (see paragraphs 3.52-3.58). (In the case of research sponsored by a NHS body, NHS indemnity will be ensured when final management permission is given for the research.)

(k) In the case of a CTIMP, the European Clinical Trials Database (EudraCT) number has been entered on the application form (at A65).

(l) The Chief Investigator is professionally based within the United Kingdom.

(m) In the case of a CTIMP, either the sponsor or the sponsor’s legal representative\(^1\) is legally established within the European Union.

(n) In the case of a CTIMP in which the sponsor has appointed a legal representative, the legal representative has provided a copy of the contract

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\(^1\) The legal representative assumes all the statutory responsibilities and legal liabilities of the sponsor in relation to the trial.
with the sponsor and evidence of insurance cover within the EU to cover the potential liability arising from the research.

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

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

(p) A covering letter has been provided, explaining how the new application addresses the reasons given for the unfavourable opinion.

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

1.50 A Part C should also be submitted if the application is to a LREC and the Chief Investigator is also the Principal Investigator for a local site covered by the LREC (“the lead site”). In such cases, the LREC should carry out the site-specific assessment (SSA) (see Section 4) for the lead site alongside the ethical review. However, no Part C is required to be submitted initially if either of the following apply:

(i) In the case of a study declared on the application form as being SSA-exempt, no Part C needs to be submitted at any stage of the process unless the reviewing REC subsequently decides that SSA is required (see paragraph 4.20).

(ii) In the case of a study with one or more Principal Investigators requiring SSA, no Part C needs to be submitted initially if the REC carrying out the ethical review is either a MREC or a LREC with no responsibilities for any of the research sites. In such cases, the Principal Investigator(s) should submit Part C to the relevant LRECs for SSA once the main REC has validated the application.

1.51 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 at A45 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.

1.52 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. 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.

1.53 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*

1.54 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
- SL2 Validation of SSA-exempt study.

1.55 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 co-sponsors should notify the REC as to which of them will be the main contact point for communications with the REC.

1.56 LREC Co-ordinators should also send a copy of the validation letter to the appropriate care organisation in the case of any single-site research, or in the case of multi-site research where it is the LREC for the lead site as well as the main REC for the application. Other care organisations at which it is planned to conduct multi-site research should be notified by the relevant LREC when the application for SSA is validated (see paragraph 4.42).
1.57 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

1.58 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. 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 60 day time period for review of the application does not start until a valid application is received.

1.59 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 by the REC office.

Applications validated in error

1.60 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.
Transfer of applications to another REC

Mandatory transfer

1.61 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 application relates to a CTIMP, and the receiving REC is not recognised by UKECA to review any CTIMP or is not recognised to review the appropriate class of CTIMP.

(b) The receiving REC is an authorised LREC (i.e., not recognised by UKECA) and the research will not be conducted within a domain(s) for which the LREC is authorised to conduct ethical review. (Exceptionally, the LREC may retain the application where arrangements have been agreed with the relevant appointing authorities for the LREC’s scope to be extended beyond its own domain.)

(c) The receiving REC is a MREC, and the application has not been booked through CAS.

(d) 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.

Optional transfer

1.62 In addition, the receiving REC may arrange for “optional transfer” of an application for one of the following reasons:

(a) The application has been submitted more than two weeks ahead of the next closing date for applications.
(b) The application has not been booked in advance and cannot be accepted because the agenda for the REC’s next meeting is full.

(c) 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.

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

(e) 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.

1.63 Optional transfers under (a) (b) or (c) in paragraph 1.62 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.

1.64 Although transfers under paragraph 1.62(a) (b) or (c) should normally be with the Chief Investigator’s agreement, the REC Co-ordinator may proceed with the transfer with the approval of the OREC Manager if the Chief Investigator cannot be contacted.

1.65 An optional transfer under paragraph 1.62(d) should take place only after consultation with the OREC Manager and with his/her agreement.

1.66 In the case of optional transfers under paragraph 1.59(d) or (e), the validation date remains the date on which it was first received by the REC that transfers the application.

Re-allocation of transferred applications

1.67 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. The applicant should be advised of the arrangements required for re-allocating.

1.68 Applicants should contact CAS about the re-allocation of any application relating to:

- Clinical trials of investigational medicinal products
- Multi-site studies to be conducted in two or more domains
- Prisoners
- Adults with incapacity in Scotland.

1.69 Applicants should contact the OREC Manager for advice on the re-allocation of applications requiring special expertise not available to the receiving REC.

1.70 In all other cases, the REC Co-ordinator should advise the applicant to approach another LREC within the domain, and provide the relevant contact details and meeting schedules. If no LREC within the domain is able to accept the application, or there is no LREC established within the domain, the OREC Manager should refer the applicant to a LREC in another domain within the OREC area or exceptionally within another OREC area.

1.71 Once the new allocation has been confirmed on RED, the electronic version of the application form will automatically be transferred. The Co-ordinator of the receiving REC should offer to forward the signed paper copy (if applicable) and the supporting documentation to the second REC.

Responsibility for validating transferred applications

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

1.73 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. The letter should carry the 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.

1.74 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.

Retention of Part C by LREC for lead site

1.75 Where the receiving REC is the LREC for the lead site and has received a Part C with the application, this should be retained together with a copy of the Principal Investigator’s CV. The LREC continues to be responsible for the site-specific assessment.

Revision of applications following submission

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

1.77 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 1.82). Any minor revisions may either be discussed at the meeting or dealt with later in accordance with paragraph 1.78.

1.78 If the applicant considers it necessary to make minor revisions to the application form or the supporting documentation following review by the REC but before a final ethical opinion has been given, these may be included in the applicant’s response to the request made by the REC for further information or clarification (see Section 3). The changes 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.

1.79 If the Chair considers the proposed revisions to be both 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 appropriate at this stage for the applicant to introduce significant new issues, which the REC will not have had the opportunity to review collectively.

1.80 When considering revisions to applications for multi-site studies requiring SSA, the main REC should also note the guidance in paragraph 4.73.

1.81 For revisions made after a favourable opinion has been given, refer to the procedures for review of amendments in Section 5. “Notice of amendment” forms should not be used until after a favourable opinion has been given.

Withdrawal of applications

1.82 If an applicant withdraws an application at any time, it should be treated as no longer valid. Letter SL26 should be sent to the applicant. If the applicant wishes to re-submit the application, it should be re-booked with the LREC or through CAS, as appropriate. A new REC reference number should be issued. A new period of 60 days commences when the valid application is re-submitted.

Applications not within the scope of a NHS REC

1.83 Where an application is received by a REC that falls outside the scope of a NHS REC as defined in GAfREC, the following procedures apply.

1.84 If the application relates to research in the field of health or social care, which (a) is not a CTIMP and (b) is outside the normal remit of a NHS REC as defined in GAfREC, the REC is not obliged to review it. However, it is desirable as a matter of public policy that such research is ethically reviewed, and RECs are encouraged to agree to review applications and give an ethical opinion on a voluntary basis. It is a

1 Where an application relates to a CTIMP, a NHS REC that is recognised by UKECA to review the appropriate class of CTIMP is generally obliged to review it even where the research is outside the scope of GAfREC.
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 following procedures apply:

- If the booking was made direct to a LREC, the applicant may approach the OREC Manager, who will decide whether or not to invite another LREC within the domain to consider the application.

- If the booking was made through CAS, the Operations Director will decide whether or not to invite another REC to consider the application.

1.85 If the application relates to a project that does not fall within the definition of research given in GAfREC, the Chair may decide that the application does not need to be submitted to a meeting of the REC. Where an application has been received to which this could apply, the Co-ordinator should send it to the Chair, who should consider the matter within 5 working days and notify the Co-ordinator whether or not it should be reviewed. If it is decided that the application does not require review, a response should be sent to the applicant using SL24. The REC is not responsible for giving an ethical opinion on the project. If, however, the application requires review, it should be validated and reviewed in the normal way.

1.86 Where the Chair or Co-ordinator is approached for advice on whether a project falls within the definition of research, and therefore whether an application should be submitted to the REC, it is recommended that the applicant is invited to provide a brief outline of the project in writing. This should then be considered by the Chair in line with the procedure in paragraph 1.85, except that the need to decide within 5 working days does not apply as no application has been submitted.

Retrospective applications

1.87 In some cases, applicants may disclose that the research has already started without first obtaining a favourable ethical opinion. Within the NHS, 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 OREC Manager and the REC’s appointing authority in accordance with the procedures in paragraphs 9.89-9.91.

1.88 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 meeting of the Committee or sub-committee.

1.89 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.
Section 2: Meetings of a Research Ethics Committee

Summary

An ethical opinion can only be given after review of an application at a REC meeting. RECs normally meet monthly. There must be at least 10 scheduled meetings each year. Additional meetings can be arranged, particularly if there is a risk of not processing an application within the 60 day deadline.

Meeting schedules and closing dates for applications are agreed with a Committee’s OREC Manager and then publicised to NHS organisations and research bodies. Schedules for recognised RECs are provided to the Central Allocation System (CAS).

The Co-ordinator arranges distribution of agenda, applications and other papers for meetings in accordance with local procedures. There should normally be a minimum of 5 and a maximum of 10 new applications for review at each meeting. The Co-ordinator should notify 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 before discussion of new applications can commence. 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 Committee’s discretion and subject to a confidentiality agreement.

Members must declare any 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 should be 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. Supervisors of student researchers may also be invited to attend.

Members who are unable to attend may send written comments prior to the meeting.

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, for example when reviewing studies that involve minors or adults incapable of giving informed consent. 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 minute-taking. The minutes should be ratified by the Committee at the next meeting. The ethical opinion given on each application should be made public in the Committee’s annual report.
Section 2  Meetings of a Research Ethics Committee

General policy

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

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 hold at least 10 scheduled Committee 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 time limit of 60 days from the date of receipt; 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 OREC Managers should ensure that the meeting schedules of LRECs 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 60 days.

2.6 The schedule of Committee meetings for the year commencing on 1 April should be agreed between the Co-ordinator and the OREC 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 no earlier than 21 days and no later than 14 days prior to each REC meeting.

2.8 Following approval by the OREC Manager, LREC 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 LREC. 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 Operations Director and CAS of their meeting schedule for the forthcoming year and any changes made during the year. The Operations Director may request changes to meeting schedules to ensure that the system as a whole has sufficient operational capacity at all times.

Agenda

2.10 The REC Co-ordinator should prepare the agenda for the meeting, which 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 Committee 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
- Report by the Co-ordinator (see paragraphs 2.15-2.20).

2.11 Where it is the local procedure to appoint lead reviewers (see paragraphs 2.21-2.22), the agenda should indicate the lead reviewer(s) for each application.

2.12 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 Committee procedures
• Training issues.

2.13 It is important that REC meetings include sufficient applications to maintain the expertise of the Committee and justify the resources involved, but not so many as to undermine the rigour of the ethical review. The agenda should normally include no fewer than 5 and no more than 10 new applications for ethical review. The local operating limits should be agreed with the OREC Manager. OREC Managers will review the workload of RECs periodically.

2.14 Section 6 describes arrangements for REC business that may be conducted by sub-committees. The agenda for Committee 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

2.15 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 (the sub-committee minutes may be appended to the Co-ordinator’s report or copied to members separately)
• Progress reports on research with a favourable opinion (see paragraph 9.14)
• Receipt of quarterly or annual safety reports on CTIMPs, and reports of Data Monitoring Committees (see paragraph 9.48)
• Notification of the conclusion or early termination of research (see paragraph 9.76)
• Receipt of final study reports (see paragraph 9.87).
2.16 It is recommended that the Co-ordinator should prepare a separate report for distribution to members with the papers for each meeting. However, it is a matter for the discretion of the REC how the information is reported, provided that it is in writing. Local procedures should be agreed. A standard report format will be made available on RED for optional use.

2.17 Where the REC has previously delegated authority to the Chair to issue the opinion of the Committee following receipt of further information or clarification from the applicant (see paragraphs 3.23-3.26), 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.

2.18 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 Committee’s requirements.

2.19 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 Committee as soon as possible, a further written report may be prepared or an oral report made to the meeting.

2.20 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 Committee and recorded in the minutes.
Lead reviewers

2.21 A REC may appoint one or more members as lead reviewers for each application.

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

Distribution of papers for meetings

2.23 The REC Co-ordinator should normally arrange for distribution of the agenda and papers for review at the meeting between 7 and 14 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 Committee.

2.24 All members should receive the application form for each new application, together with all supporting documentation except as follows:

- The protocol for the study should be sent only to the lead reviewer(s) and to members with relevant expertise. Other members should not normally need to see the protocol but should be provided with a copy if they request it.

- The Investigator Brochure for an investigational medicinal product should be sent only to members with relevant expertise (in particular, to the pharmacist or clinical pharmacologist).

Attendance of the Chief Investigator

2.25 The Chief Investigator should be invited to attend the meeting at which his/her application is to be reviewed. The purpose of this is to be available to respond directly to requests from the Committee for further information, clarification or reassurance. In this way, many issues of concern to the Committee may be resolved at the meeting. Even where further consideration needs to be given by the Chief
Investigator after the meeting to matters raised by the Committee, his/her attendance to hear the points raised in person may well prove to have been helpful in formulating a satisfactory response.

2.26 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.

2.27 Where the Chief Investigator is unable to attend, it is acceptable for another key investigator or collaborator to attend instead. It is not generally acceptable for a representative of the sponsor to attend in place of the Chief Investigator, but the Chair may allow this in exceptional circumstances. Other members of the research team or representatives of the sponsor may also express an interest in attending alongside the Chief Investigator, and this should normally be permitted if the size of the meeting room makes it practicable.

2.28 Where speakerphone facilities are available in the room to be used for the meeting, the REC may offer the Chief Investigator the alternative of being available by phone at the time of the review. It should be possible for all members present in the room to question the Chief Investigator and hear the responses.

2.29 In the case of applications submitted by students, the REC should consider inviting the educational supervisor to attend. In addition, where the student is conducting the research under supervision within the NHS, the clinical supervisor may be invited to attend.

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

Quorum requirements and meeting attendance

2.31 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
• One expert member.

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 Committee 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
• Deputy members attending alongside the lead member.

2.35 Where a quorum is not present, the Committee may not commence, continue or conclude any discussion with the purpose of determining the Committee’s opinion on an application for ethical review.

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...

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1 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 COREC website.
be attended by a quorum of members due to foreseen absences, he/she should consider the following options with the OREC Manager:

- Co-opting up to two additional members (see paragraphs 2.40-2.42)
- Postponing and re-arranging the meeting
- Cancelling the meeting.

2.39 If the meeting is postponed or cancelled, the Co-ordinator should consider with the OREC 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. A person may be co-opted as a member only if he/she is or has been a member of a REC. 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.

2.41 Local procedures for co-opting members within each domain or OREC area are the responsibility of the OREC Manager. The OREC Manager should maintain records of members within the area who would in principle be willing to be co-opted where required. The form of indemnity issued for these members by the appointing authority should clarify that they are indemnified for their actions as co-opted members of other RECs within the domain as well as of the REC to which they are appointed.

2.42 Arrangements should be made to provide a statement of indemnity from the appointing authority, prior to the meeting if possible, in the following cases:

(a) The co-opted member is a former member of a NHS REC, and the indemnity from the appointing authority no longer applies

(b) The co-opted member is a serving member of a NHS REC in another domain, and his/her indemnity does not extend to service on RECs outside the domain.
Written comments from members

2.43 A 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 the submission of written comments.

2.44 A member who submits written comments but does not attend the meeting 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.

2.46 Referees are not voting members of the REC, and should not be involved in the business of the Committee 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 Committee may decide at the meeting to seek *written advice following the meeting*. The Co-ordinator or Chair should normally write to the referee within 5 days of the meeting using SL8. The written advice received should then be considered promptly at a meeting of the sub-committee.

(iii) 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 Committee.

2.48 The 60 day clock for ethical review does not stop while the advice of a referee is sought (see paragraphs 3.34-3.40).

*CTIMPs involving minors or adults with incapacity*

2.49 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.

2.50 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.

2.51 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.

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

2.53 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.
2.54 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 tables at the meeting. The substance of the advice should be recorded in the minutes.

2.55 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 OREC Manager whether a suitably qualified member or previous member of another REC may be co-opted.

- The Co-ordinator may explore with CAS 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 an opinion until it has consulted a referee following the meeting, in accordance with paragraph 2.47(ii).

2.56 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.

Declarations of interest

2.57 Members and deputy members should declare to the Committee any 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.

Applications for ethical review

2.58 Where the member concerned is the Chief Investigator or another key investor/collaborator named on the application form at A66, the Committee should
not proceed with the review, and arrangements should be made urgently for the application to be transferred to another REC.

2.59 In the case of any other declared interest, the Committee should collectively consider whether or not 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.

2.60 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.

2.61 The minutes should record any declaration of interest and the decision of the Committee 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 2.60(i) above.

Site-specific assessments

2.62 Where a member or deputy member of a LREC is named on Part C of the application form as the Principal Investigator or another member of the local research team, the procedures in paragraph 4.51 apply.

Confidentiality of proceedings

2.63 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.

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

Observers

2.65 Observers may be invited to attend Committee 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 Committee 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.

2.66 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 2.27, rather than as an observer.

2.67 Meetings, or parts of meetings, may also be attended from time to time by representatives of appointing authorities, OREC Managers, peer reviewers, and other senior staff from COREC in accordance with governance arrangements for RECs (“official observers”). Arrangements for attendance should be discussed and agreed beforehand with the Chair.

2.68 If an 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 any 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

2.69 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 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.

2.70 All members present, both expert and lay, should be allowed reasonable opportunity to express relevant views on matters on the agenda.

2.71 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.

2.72 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

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

2.74 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 (where this is the practice of the REC).
(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 OREC 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.

(xi) Making a written record of the meeting.

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

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

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**Minutes**

2.75 The minutes of the REC meeting should be prepared by the secretary to the meeting. It is not mandatory for the minutes to be formally approved by the Chair before letters are issued to applicants giving the Committee’s decision, though it is good practice for the Co-ordinator to check the drafting of technical or sensitive issues with the Chair and/or other relevant members if in doubt. Local procedures should be agreed.

2.76 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 2.57-2.61).

(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)).

(vi) The decision of the REC on the application (see paragraph 3.6).

(vii) A summary of the main ethical issues considered (see paragraph 3.15).
(vii) The decision of the REC on whether site-specific assessment is required, where the criteria for exemption from SSA may apply to the application (paragraphs 4.19-4.32).

(viii) In the case of a favourable opinion, any special approval conditions (see paragraph 3.18) or additional advice to be given to the applicant.

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

(x) 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 3.8-3.10 and 3.23-3.31).

(xi) Where no opinion is given, the issues on which further advice is required from a referee (see paragraph 3.38).

(xii) 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 paragraph 5.48).

(xiii) The outcome of any vote taken.

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

2.77 Except where (xiv) 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.

2.78 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.

2.79 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, the OREC Manager or peer reviewers undertaking accreditation on behalf of COREC.

2.80 The opinion of the REC on each application for ethical review should be published in the annual report. Further guidance on annual reports is set out in GAfREC.
Section 3: Giving an ethical opinion

Summary

Under the EU Directive and the Clinical Trials Regulations a REC must give an opinion on a CTIMP within 60 days of receipt of a valid application. Departmental policy is to apply the same process to all other research reviewed by NHS RECs. For some specialised clinical trials, the Clinical Trials Regulations specify different time limits for review.

Where a REC requires further information before confirming its opinion, it may make one request only for further information in writing to the applicant. While the REC waits for the applicant to respond, the 60 day clock stops. When the REC receives all the further information it requested, the clock starts again.

GAfREC defines the ethical issues that need to be considered in the ethical review of research. This section of the SOPs describes the procedures for giving an ethical opinion. The SOPs do not circumscribe the responsibility of RECs for deciding what is ethical.

A REC should reach one of four possible decisions following ethical review:

- Final opinion - this could be favourable or unfavourable
- Provisional opinion - with request for further information, clarification or revision
- No opinion - a referee needs to be consulted before an opinion can be given.

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 meeting, or exceptionally a meeting of the Committee.

If no opinion is given, 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. On receipt, the application should be reconsidered at a sub-committee or Committee meeting.

The Co-ordinator notifies the Chief Investigator of the decision reached within 10 working days of the meeting. A standard letter for each type of opinion is obtained from RED. A final favourable opinion letter should enclose standard conditions of approval to which the researcher must adhere. The REC may add study-specific approval conditions if appropriate. Reasons for unfavourable opinions should be fully explained.

Before commencing a CTIMP, the sponsor must obtain clinical trial authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA). The CTA application may be made in parallel with the REC application. It is not necessary to have a CTA in order to obtain a favourable opinion, but the REC should be provided with evidence of the CTA when available. Similar procedures apply to regulatory approval for medical devices or use of radionuclide materials. Guidance is given on insurance or indemnity arrangements.

Correspondence relating to the ethical opinion should be copied to the sponsor. The local R&D Department should also be kept informed. For a CTIMP the MHRA must be notified of the final opinion. The final opinion is a matter of public record.
Section 3  Giving an ethical opinion

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 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 somatic cell therapy, or (b) a medicinal product containing a genetically modified organism, 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 Department of Health and the devolved administrations is that these requirements will also apply to all other research reviewed by RECs.

3.5 Guidance on the matters to be considered in the ethical review of research is set out in GAfREC. This section of the SOPs sets out the procedures to be followed in communicating decisions made at meetings, requesting further information from applicants and issuing the REC's opinion. It does not in any way constrain the independence of the REC in considering the ethics of individual research applications and deciding whether or not to give a favourable opinion.
Decisions available to the REC

3.6 A REC should reach one of the following decisions on any application reviewed at a meeting:

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

   (a) favourable
   (b) unfavourable.

(ii) **Provisional opinion with request for further information.** The Committee may decide that an opinion cannot be issued until further information or clarification has been received from the applicant (see paragraph 3.8-3.9). It should indicate a provisional opinion at the meeting.

(iii) **No opinion.** The Committee may decide that no opinion can be given until a referee has been consulted (see paragraphs 3.34-3.40).

3.7 The Chair should ensure that one of the above decisions is made on every application considered at a REC meeting.

3.8 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 at the meeting.

- Delegation of responsibility for considering the further information and issuing the REC’s opinion is clearly agreed (see paragraphs 3.23-3.31).

3.9 Requests for further information or clarification may include recommendations for revision of the terms of the application or any of the supporting documentation, for example the participant information sheet and consent form.
3.10 The secretary to the meeting 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.

3.11 The decision taken on each application at the meeting should be entered on RED.

**Notification of the decision to the Chief Investigator**

3.12 The Co-ordinator should ensure that notification of the decision is sent to the Chief Investigator in writing within 10 working days of the meeting. All letters should be in the name of the Chair, who has ultimate responsibility for 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 2.75). One of the following letters should be used:

- SL5 Favourable opinion
- SL6 Unfavourable opinion
- SL7 Provisional opinion with request for further information
- SL8 No opinion pending consultation with a referee.

3.13 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.
- Any interests declared by members who were present for the discussion of the application.
- The names of any observers present at the meeting.
3.14 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).

3.15 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.

3.16 The letter should not attribute particular comments or questions to individual members of the Committee.

**Final opinion letters**

3.17 All letters issuing the REC’s final opinion should be in the name of the Chair. 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 Chair has ultimate responsibility for the content.) The letter should be posted to the applicant no later than 60 calendar days from the validation date.

3.18 Where the final opinion is favourable, the applicant should also be sent the standard conditions for research approved by a REC. The Co-ordinator should enclose either SL-AC1 (clinical trials of investigational medicinal products) or SL-AC2 (all other research). Any additional approval conditions specified by the REC for a particular application, for example a requirement for more frequent progress reports, should be included in the letter. In addition to the approval conditions, the REC may give advice that is not binding on the applicant.

3.19 In the case of studies requiring site-specific assessment (SSA), the REC reviewing the application (“the main REC”) is also required to confirm approval of each site as part of the ethical opinion. The Co-ordinator should enclose form SF1 listing the approved sites (see paragraph 4.64) with the favourable opinion letter.
3.20 Where the main REC is not an LREC 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 carried out. In such cases, the Co-ordinator should issue the favourable opinion without delay (see paragraph 4.65). Form SF1 does not need to be raised at this point.

3.21 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).

3.22 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.

Provisional opinion and request for further information

Delegation of responsibility by the REC

3.23 Where the REC requests further information from the applicant, it should decide at the meeting the procedures for considering that information and for issuing the REC’s final opinion. These responsibilities should normally be delegated to one of the following:

(i) Chair alone, with support from REC office staff;

(ii) 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 meeting.

3.24 In deciding the procedures to be followed, the REC 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 meeting should be arranged so that they can be fully discussed.

3.25 Where responsibilities for review of information are delegated to REC office staff, the Chair remains ultimately accountable for the opinion of the Committee.

3.26 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 60 day 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 60 day time period

3.27 The 60 day time period 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”).

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

3.29 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.

Requirement for a complete response

3.30 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, setting out the further information or clarification still required. (SL11 may be issued more than once if the response continues to be incomplete.) The REC is not entitled to raise
any new issues or concerns at this stage of the process. The 60 day time period should remain suspended until a complete response is received.

3.31 The applicant should be allowed a period of four months to respond to the request for further information. If the applicant has not responded within three months of the date of the request, 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.

3.32 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.

Final opinion following consideration of the information

3.33 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
SL15 Unfavourable opinion following consideration of further information

Further advice from a referee

3.34 Where a REC decides that it cannot give an opinion until it has obtained further advice from a referee, the following procedures should be adopted.

3.35 Letter SL8 should be sent to the applicant following the meeting, explaining that no opinion has been given on the application pending consultation with a referee. The letter may notify the applicant of the issues of concern to the REC, but should not at this point request further information or clarification.
3.36 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 OREC Manager, who may be aware of REC members elsewhere in the domain with the relevant expertise, or from senior operational management at COREC. The referee may be another REC or specialist body.

3.37 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 paragraph 3.40).

3.38 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.

3.39 Once the referee’s advice has been received, it should be considered at a meeting of the sub-committee (see Section 6), or at a further meeting of the REC if time allows. The REC should either decide to give an opinion on the application at this point, or request further information from the applicant. Where a favourable or unfavourable opinion is given, SL5 or SL6 should be used and the procedures set out in paragraphs 3.17-3.22 apply. Where further information is requested, SL10 should be used and the procedures set out in paragraphs 3.23-3.32 apply.

3.40 The REC should not disclose the nature of the referee’s advice to the applicant. The opinion it reaches on the application is its own. It may not disclose the identity of the referee except with his/her express permission.

Regulatory approval

3.41 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. Applications for regulatory approval may proceed in parallel with the ethical review. 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.

Clinical trials of investigational medicinal products

3.42 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).

3.43 The application for CTA may be made either in parallel or in sequence with the application for the ethical opinion. It is not essential to have the CTA in order to make a valid application to the REC or to obtain a favourable ethical opinion. The REC should be provided with evidence of the CTA when available, either in the course of the ethical review or following the issue of the ethical opinion.

3.44 Where a favourable ethical opinion is given before the CTA, and the MHRA attaches conditions to the CTA requiring significant changes to be made to the terms of the REC application or the supporting documentation, a notice of amendment form should be submitted to the REC for review (see Section 5).

3.45 Where the MHRA rejects the application for CTA, it will require the sponsor to notify the main REC.

Medical devices

3.46 For a study involving a CE Marked device being used for its intended purpose, the sponsor does not need prior regulatory approval from the MHRA (which is the UK competent authority both for medicines and devices).
3.47 For a clinical investigation involving a non-CE Marked medical device (i.e. a new or substantially modified device, or an existing device with new function, feature or material) or a CE Marked device being used for a new intended purpose, the sponsor is required by the Medical Devices Regulations 2002 to obtain a Notice of No Objection from the MHRA prior to commencing a study (see Part B Section 2 of the REC application form).

3.48 The application for MHRA review of the clinical investigation may be made either in parallel or in sequence with the application for the ethical opinion. It is not essential to have the Notice of No Objection in order to make a valid application to the REC or to obtain a favourable ethical opinion. 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.

3.49 Where a favourable opinion is given before a Notice of No Objection is issued, and the sponsor has agreed amendments to the study with MHRA that require significant changes to be made to the terms of the REC application or the supporting documentation, a notice of amendment form should be submitted to the REC for review (see Section 5).

3.50 Further information about the system of regulatory approval for devices is at Annex G.

ARSAC certificates

3.51 Where the study involves the use of radionuclide materials, this must be covered in the certificate held by the ARSAC certificate holder. If the study involves additional radiation from a current technique, a new agent, or a novel use of an existing agent, a further certificate must be obtained (see Part B Section 3 of the application form). It should be assumed that this will be obtained before the study commences. It is not essential to provide a copy of the ARSAC certificate in order to obtain a favourable ethical opinion.

Insurance and indemnity

3.52 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). Information about insurance or indemnity arrangements is required in the REC application form (see A35 and A36).

3.53 Non-NHS sponsors must provide evidence of insurance cover (see paragraph 1.48(j)). Before confirming a favourable opinion, the REC should ensure that it has received documentation from the sponsor confirming that it has appropriate insurance cover for the potential liability arising from the research. The documentation should make clear the extent of the cover and the source of the funds. (For student research, see paragraph 3.56.)

3.54 Site Management Organisations, or other Principal Investigators responsible for conducting research at sites outside the NHS, should also provide evidence of insurance or indemnity cover with the application for site-specific assessment (see paragraphs 4.41 and 4.44).

3.55 In the case of NHS-sponsored research, NHS indemnity will be ensured when final management permission is given for the research by the care organisation. This will occur after the issue of a favourable opinion.

3.56 For student research sponsored by an educational institution, the applicant should either arrange for signature of the declaration at A71 on the application form, or provide other documentary evidence of insurance or indemnity from the institution. For student research sponsored by a NHS organisation, paragraph 3.55 applies.

3.57 In the case of commercially sponsored CTIMPs or medical device studies, compensation to participants may be available under the Association of British Pharmaceutical Industry (ABPI) or Association of British Health-Care 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, and a copy of the model form of indemnity to be used.

3.58 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. Nor, in the case of multi-site studies, is it
necessary for LRECs to check that this documentation is in place as part of the site-specific assessment, except for non-NHS sites (see paragraph 3.54).

Further review following an unfavourable opinion

3.59 Where a REC has given an unfavourable opinion on an application, the applicant may seek further review as follows:

- A new application may be submitted, taking due account of the REC’s concerns. This should be processed and reviewed in the same way as any other new application.

- A second review of the same application may be obtained from another REC by giving notice of appeal to COREC.

3.60 Procedures relating to further review are set out in Section 7.

Communication with other bodies

3.61 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 COREC is that the REC system should take reasonable steps to facilitate good communication between those concerned.

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

(i) The main REC should send the sponsor (or 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 main REC is also the LREC for the lead NHS site, it should send copies of correspondence to the R&D Department for the care organisation or consortium. 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) LRECs undertaking site-specific assessment should send a copy of the letter validating the SSA (SL17) to the research governance contact for the care organisation or consortium. The Chief Investigator and sponsor will be expected to arrange for care organisations to be notified of the decision of the main REC following SSA.

3.63 In the case of any CTIMP, the main REC is required by the Clinical Trials Regulations to notify the MHRA of the final opinion. A copy of the final opinion letter should be sent to the following address:

Clinical Trials Unit  
Medicines and Healthcare products Regulatory Agency  
Market Towers  
1 Nine Elms Lane  
London SW8 5NQ

3.64 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 include an appropriate statement of compliance with ICH 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 explains that the constitution of a NHS REC is as defined in GAfREC and its operating procedures are defined by the national SOPs issued by COREC. No additional documentation needs to be provided to sponsors. In particular, there is no requirement to provide details of LREC members or other individuals involved in site-specific assessments.

3.65 Guidance on the publication of decisions in the REC’s annual report is set out in GAfREC.
Approval to proceed with research

3.66 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 Departments 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.

The single ethical opinion includes an opinion on each site and investigator taking part in the research (unless it is “SSA-exempt”). The REC undertaking the ethical review (the “main REC”) is responsible for all aspects of the review, taking advice on the suitability of sites and investigators from other relevant LRECs. The process of site-specific assessment (SSA) by LRECs 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-exempt” studies are those involving routine or low risk research procedures (defined in this section) that do not require the appointment of Principal Investigators at each site. The applicant may declare a study as SSA-exempt. This must be confirmed by the main REC when giving the ethical opinion. Studies designated as SSA-exempt do not require SSA by LRECs or approval of individual sites by the main REC.

Local Principal Investigators may submit applications for SSA as soon as the main application for ethical review has been validated. The application comprises Part C of the application form and the PI’s CV. Additional documentation is required for non-NHS sites.

Guidance is given on issues relevant to the SSA. The LREC 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.

SSAs may be considered at Committee or sub-committee meetings, or in correspondence involving at least 2 members including the Chair. The PI may be invited to attend a meeting. Clarification of issues relevant to the SSA may be sought.

The SSA may be delegated to another assessor such as local R&D but the LREC remains responsible for communicating decisions to the main REC using RED. The OREC Manager is responsible for drawing up a written agreement with the assessor.

The LREC has 25 days 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. Form SF1 is used to list approved sites. The CI is responsible for notifying each PI when the site has been approved.

Neither the main REC nor the LREC 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 LREC may itself instigate a new SSA and should report any new concerns to the main REC.
Section 4  Site-specific assessment

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 to all multi-site research within the UK.

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.

Site-specific assessment

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

4.5 SSAs will be undertaken either by the LREC for the relevant geographical area or by another local assessor appointed by the OREC Manager. In the case of single-site or multi-site research studies where the main REC is also a relevant LREC for a site, it may undertake the SSA itself alongside its consideration of the application. In all other cases, the SSA for each site will be undertaken separately, and the outcome notified as advice to the main REC from the LREC. As far as possible, SSAs should be undertaken in parallel with the consideration of the application by the main REC and within the 60 day time period, so that the approved sites can be listed when issuing a favourable opinion. In certain circumstances, however, SSAs may be
carried out subsequently, and the list of approved sites for the study updated by the main REC.

The Principal Investigator

4.6 In the case of any single or multi-site research requiring SSA, 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.

4.7 A “single site study” is a study that the Chief Investigator plans to conduct at one site only in the United Kingdom. If the study requires SSA, the Chief Investigator will in most cases also be the Principal Investigator for the site.

4.8 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 if the research procedures require SSA (see paragraphs 4.19-4.32). 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).

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

Definition of a research site

4.10 Under the Clinical Trials Regulations, a “trial site” means a hospital, health centre, surgery or other establishment or facility 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. The guidance should be taken into account by applicants and RECs in relation to:

- identifying the individual sites at which the research is to be conducted
- appointing a Principal Investigator (where SSA is required)
- applying for SSA (entering the name of the site on Part C of the application form)
- giving an ethical opinion for each site.

4.11 In general, the research site should be identified as the single organisation responsible for conducting the research at a particular locality.

4.12 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 Personal Social Services Trust (in Northern Ireland)
- A GP practice.

4.13 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.

4.14 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.

4.15 For research conducted by GPs, 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 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 are conducting a study within the same GP practice, the practice should be regarded as a single site and one of the GPs should be appointed as the Principal Investigator.

• In some cases, two or more independent GP 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 GP 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 may also be involved in the network/consortium.

4.16 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.

4.17 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.

4.18 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)
• a private hospital or private clinical practice.

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), the name of the site should be clearly distinguished from the NHS organisation concerned.

Exemption from site-specific assessment

Responsibilities of the main REC

4.19 The need for site-specific assessments to be carried out in the case of multi-site studies is a matter for the discretion of the main REC, taking into account the guidance in paragraphs 4.24-4.32. The guidance applies to both single- and multi-site studies.

4.20 When submitting an application, the Chief Investigator should declare (at A6 on the application form) if in his/her opinion the research does not require SSA at any research site. Where such a declaration is made, this should be considered by the main REC at the meeting at which the application is ethically reviewed. The REC should consider the procedures to be carried out and decide whether SSA is required. The decision should be one of the following:

(a) SSA-exempt. All sites in the study are exempt. There is no requirement for Principal Investigators to be appointed at individual sites or for any Part C to be submitted as part of the application. No research site requires specific approval as part of the ethical opinion for the study. The main REC will assess the suitability of the Chief Investigator, and his/her research facilities, as part of the main ethical review. The information provided in Parts A and B of the application form and supporting documentation should normally be sufficient for this purpose. Aggregated information about recruitment of local research sites should be provided to the main REC in annual progress reports.

(b) Non-exempt. In general no sites are exempt. A Principal Investigator should be appointed at each site and an application made for SSA. Specific approval for each site should be given by the main REC as part of the ethical opinion.
(Exceptionally, individual sites in a non-exempt study may be specially exempted from SSA by decision of the main REC – see paragraph 4.32.)

4.21 After the meeting the Co-ordinator should notify the Chief Investigator of the decision of the REC. The outcome should be entered on RED.

4.22 In the case of SSA-exempt studies, no information about the study needs to be provided to other RECs. However, local collaborators should still seek research governance approval from the R&D Department for the care organisation. Where the Chief Investigator is conducting the research directly at a number of sites, he/she also requires research governance approval from the R&D Department for each care organisation.

4.23 The main REC may review SSA exemption at any time. In particular, it may be appropriate to review the designation of some multi-site studies that received ethical approval prior to 1 March 2004 in the light of the guidance in paragraph 4.24-4.32. A decision to change the designation of a study should be taken at a sub-committee or Committee meeting. The Chief Investigator may seek a review of the designation of the study by writing to the main REC.

Research procedures requiring SSA

4.24 In deciding on the need for site-specific assessment at particular sites, the main REC should consider:

(a) whether the site has direct involvement with participants, and
(b) whether participants may be placed at more than minimal risk of physical or emotional harm as a result of the research procedures.

The following guidance should be taken into account. If in doubt, the main REC should require SSA to be carried out.

4.25 It is mandatory for Principal Investigators to be appointed, and SSA carried out, in the case of any research sites conducting one or more of the following procedures:
(a) **Novel clinical interventions**

This includes the administration of any investigational medicinal product or any other physically invasive clinical intervention, such as surgery, which is not already established as routine clinical practice.

It also includes the use of any novel mental health intervention.

(b) **Novel clinical assessments**

This includes any physically invasive procedure carried out for the purpose of assessment or diagnosis that is not within the routine professional competence of the health care staff that will be involved in the research at the site.

It also includes the administration of any novel mental health assessment tool by a trained mental health professional.

(c) **Medical devices**

This includes any use, in a clinical investigation, of a non-CE marked medical device or a CE marked device that has been substantially modified or is being used outside the use for which it was intended.

(d) **Additional clinical monitoring**

This includes procedures for monitoring the subject and providing data to investigators, which would be additional to the collaborator's normal clinical responsibilities for monitoring their patients and involve the analysis and interpretation of clinical data in accordance with the protocol.

4.26 Where any of the above procedures are to be carried out at local sites directly by the Chief Investigator's team, a Principal Investigator should be appointed for each site and an application for SSA submitted. The Chief Investigator or another member of his/her team may act as the Principal Investigator for a number of different sites.

Where a regional unit has clinical responsibility for the conduct of trials at “shared
care” centres, the regional clinical lead should be named as the Principal Investigator and apply for SSA at each centre as a separate site.

Research procedures not requiring SSA

4.27 SSA should not normally be required where the procedures to be carried out at research sites by local collaborators or by members of the Chief Investigator’s team are limited to one or more of the following:

(a) **Routine investigations or assessments**

This includes any physical investigations, such as taking blood or urine samples, which would be within the routine professional competence of the local collaborator or researcher.

It also includes any routine mental health assessments to be carried out by a trained mental health professional, for example the administration of a validated depression scale.

(b) **Questionnaires and surveys**

Members of the Chief Investigator’s team should normally be permitted to undertake questionnaires and surveys at all sites without the need for SSA. The information provided in Parts A and B should be sufficient to assess the competence of the Chief Investigator to undertake the research at any site.

In multi-site studies, local collaborators may also administer simple questionnaires or surveys on behalf of the Chief Investigator without the need for SSA. The main REC should be assured about the arrangements for selecting and training collaborators and for the oversight of the research by the Chief Investigator.

(c) **Qualitative research methods**

SSA is not normally required but the main REC should consider the general arrangements proposed for the conduct of the study at local sites, taking into account any risk of significant harm to participants.
Members of the Chief Investigator’s team should normally be permitted to undertake qualitative research directly at all sites without the need for SSA. The information provided in Parts A and B should be sufficient to assess the competence of the Chief Investigator to undertake the research at any site.

Where significant responsibilities are delegated to local collaborators, however, and there is concern about their suitability or the local arrangements for supporting the research, the main REC may require the appointment of Principal Investigators and application for SSA at each site.

(d) Collection of data or human tissue

This includes any release of personal data or tissue samples in accordance with procedures described in the protocol and/or Parts A and B of the main application form.

(e) Routine clinical monitoring

This includes any monitoring of participants and provision of clinical data to investigators, which would be within the collaborator’s normal clinical responsibilities. For example, care professionals may provide additional data in the follow-up phase of a clinical trial with long-term efficacy endpoints.

It does not include additional clinical monitoring or assessment in accordance with a protocol.

(f) Laboratory tests and analysis

Scientific laboratories undertaking tests or analyses in support of the investigators do not require SSA.

(g) Facilitating the recruitment of participants

Local collaborators may carry out ethically approved procedures to bring the research to the attention of potential participants and facilitate their recruitment by the Chief Investigator’s team. This includes the forwarding of information sheets or recruitment
packs, display of advertising material, or promotion of the research in the media. Postal consent forms may be returned via local collaborators.

Where such procedures are delegated to local collaborators, the Chief Investigator’s team or other approved Principal Investigators should normally retain full responsibility for the informed consent process, in particular for answering participants’ questions about the research and taking written consent whether in person or by post (see paragraphs 4.29-4.31).

4.28 Any procedures to be undertaken at local sites without SSA must still have a favourable ethical opinion from the main REC, and should be fully described in the protocol or the terms of the application. The main REC may attach specific approval conditions to the ethical opinion, relating to the conduct of the research at local sites. Research governance approval should also be obtained from the relevant NHS care organisation before any research procedures are undertaken at a site, whether by local collaborators or by members of the Chief Investigator’s team.

Informed consent

4.29 It is recommended that Principal Investigators should normally be appointed, and SSA carried out, where there is delegation of responsibility to local collaborators to give information about the research to potential participants (other than forwarding information provided by the Chief Investigator), to answer their questions, or to take written consent from them. Any actions that fall directly within the informed consent process normally require the appointment of a Principal Investigator.

4.30 However, the degree of responsibility assumed by local collaborators may vary significantly according to the nature of the study, and it is for the main REC to evaluate whether SSA is necessary in these cases.

4.31 The requirement for SSA may also be waived where informed consent is to be carried out at other sites directly by the Chief Investigator’s team or other approved Principal Investigators without involvement of local research collaborators and, in the judgement of the main REC, no site-specific issues are likely to arise.
Exemption of individual sites

4.32 There may be cases in which the procedures to be carried out vary between sites according to their level of involvement in the research. In a study designated as generally “non-exempt”, the Chief Investigator or sponsor may ask the main REC to exempt particular sites from SSA if the procedures to be conducted fall within the criteria in paragraph 4.27. For example, 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 procedures such as scans, blood tests and follow-up monitoring to be carried out at other hospitals or GP practices in support of the research. (This may also be more convenient for patients.) If the procedures are within the protocol, these centres are technically research sites involved in the conduct of the research. Research governance approval from relevant care organisations will be required. However, the main REC may individually exempt such sites from SSA. A letter recording the decision should be sent to the Chief Investigator and sponsor. The sites concerned should be listed as approved on form SF1 (see paragraph 4.64) with a note to the effect that SSA is not required.

Application for site-specific assessment

4.33 Applications for SSA may be made by local Principal Investigators at other 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 site-specific assessments should normally proceed in parallel, so that the outcome of the assessments can be included in the ethical opinion given by the main REC within the time limit of 60 days.

4.34 The Principal Investigator should send the application for SSA to the relevant Local Research Ethics Committee with area responsibility for the site. OREC Managers are responsible for ensuring that all research sites within their areas, including sites outside the NHS (see paragraph 4.38), are allocated to a particular LREC for the purposes of SSA.
4.35 The LREC Co-ordinator should enter all SSA applications on RED. The SSA will be allocated a local reference number in addition to the main REC reference number for the study.

4.36 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 be encouraged to contact the LREC office beforehand so that advice can be given about local arrangements for SSAs.

4.37 In the case of CTIMPs, all LRECs are authorised to carry out site-specific assessments. As the SSA is advice to the main REC, rather than an ethical review, there is no need for the LREC to be recognised by UKECA.

4.38 If a CTIMP is to be conducted at one or more sites outside the NHS, the recognised REC that reviews the application has a statutory duty to give an ethical opinion for each site. The relevant LREC should carry out the SSA on such sites where this applies. In the case of other types of research, the NHS REC system is not obliged to give an ethical opinion on the suitability of sites outside the NHS. However, if the application has been accepted for ethical review, an opinion on all sites should normally be given. Relevant LRECs should therefore carry out SSAs on sites outside the NHS if requested.

4.39 Where the main REC is also the relevant LREC for the lead site, it should carry out the SSA for this site alongside the ethical review.

4.40 A site-specific assessment may be made either by the LREC itself or by another assessor that is approved for this purpose by the OREC Manager (see paragraphs 4.58-4.61). However, even where the SSA is delegated to another assessor, the LREC remains responsible for the process. The application for SSA should be submitted to the relevant LREC in all cases.

4.41 The application should be accepted as valid if it meets all the following criteria:

(a) Part C of the standard application form has been submitted.
(b) All relevant sections and questions in Part C have been completed, and the text is in English and legible.

(d) The application form has been signed by the Principal Investigator.

(e) Short curriculum vitae (maximum two pages) have been submitted for the Principal Investigator. (It is not necessary to submit CVs for other staff.)

(f) The name of the site has been correctly stated on the form (in response to C9), taking into account the guidance in paragraphs 4.10-4.18.

(g) Evidence of insurance or indemnity cover for the Principal Investigator has been provided (for non-NHS sites only).

(h) Evidence of professional registration for the Principal Investigator has been provided (for non-NHS sites only).

4.42 If the application is valid, the LREC Co-ordinator should acknowledge receipt by writing to the Principal Investigator using SL17. For NHS sites a copy of this letter should be sent to the research governance contact for the care organisation or consortium.

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

Issues relevant to the site-specific assessment

4.44 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:

(a) 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 clinical responsibility for the local research
team.

(b) The adequacy of the local facilities available for the research.

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

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

(e) The local arrangements for making legal representatives available to give informed consent on behalf of minors or adults unable to consent for themselves, where this is a legal requirement for the research. This includes consideration of the appointment and training of legal representatives. The LREC may request additional documentation where appropriate.

(f) 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 A29 of the application form that such groups are to be excluded, this is an ethical issue for the main REC rather than the LREC. However, if the main REC does not accept the reasons given in A29 and requires their inclusion, Part C of the form should be revised and new applications for SSA should be made.)

(g) Specific assurances may be sought that the following site-specific information will be included in the local version of the information sheet for the study or provided as additional standard information for local research participants:

- The address and telephone number of the site (normally to be included on the headed paper to be used locally)
- Contact details for the local investigator(s) and, if applicable, other staff such as research nurses
- Emergency contacts if appropriate
• Contact information for complaints and, where appropriate, independent advisers.

(h) In addition, where the research site is outside the NHS:

• Assurances may be sought that this will be made clear to participants in the informed consent process.
• Evidence should be obtained of insurance or indemnity to cover the potential liabilities of the Principal Investigator.
• Evidence should be obtained that the Principal Investigator has appropriate professional registration.
• Additional documentation may be requested relating to the governance of the research site.

4.45 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 4.50).

4.46 For research sites in the NHS, site-specific assessment does not involve consideration of general issues of research governance. Principal Investigators will send a copy of Part C to the R&D lead in the care organisation or consortium as part of the application for research governance approval to conduct the research. It is the responsibility of R&D to ensure that adequate governance arrangements are in place for the research site as defined in the application. For research sites outside the NHS, however, it may be appropriate to request additional documentation (see paragraph 4.44(h)). This could include copies of internal SOPs, protocols, quality standards, job descriptions, training policies, and evidence of audit and inspection.

4.47 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 documentation relating to the main application.
Procedures for site-specific assessment by a LREC

4.48 The site-specific assessment will be carried out by the LREC, unless responsibility is delegated to another assessor (see paragraphs 4.58-4.61).

4.49 Where the LREC carries out the SSA, 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 LREC.

4.50 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 LREC. Any relevant questions or concerns should be addressed appropriately with the Principal Investigator (see paragraph 4.52). 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 ensure that records are kept of the comments of all members concerned. The outcome of the assessment and the names of the members involved should be recorded in the Co-ordinator’s next report for the REC (see paragraphs 2.15-2.20).

4.51 Where the Principal Investigator or another member of the local research team named in Part C of the application form is a member or deputy member of the LREC, the SSA should normally remain the responsibility of the LREC 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.

4.52 Every effort should be made to address relevant questions with the Principal Investigator within the 25 days 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 4.70).
4.53 The LREC should ensure that the assessment is made and the main REC notified of the outcome within 25 days of receipt of a valid application. It is generally the responsibility of the OREC Manager to monitor achievement of the 25 day target, using management information on RED. If in a particular case the main REC has not been notified of the outcome within 25 days, the Co-ordinator may follow this up directly with the LREC Co-ordinator by e-mail, with a copy to the OREC Manager. It is the OREC Manager’s responsibility to investigate further and ensure that the outcome of the SSA is notified as quickly as possible.

4.54 Where the LREC has no objections to the research on site-specific grounds, the LREC Co-ordinator should enter this on RED, which will notify the Co-ordinator of the main REC electronically. If RED cannot be used for this purpose, for example where the SSA is being provided to an ethics committee outside the NHS REC system (see paragraph 4.90), the LREC Co-ordinator may send SL19 by letter or e-mail.

4.55 Where the LREC has objections on site-specific grounds, the LREC Co-ordinator should write to the main REC by e-mail using SL20, giving specific reasons for the objections.

4.56 The LREC (or other assessor) 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 4.70-4.71). The Principal Investigator will be notified of the outcome in due course once the main REC has informed the Chief Investigator (see paragraph 4.66).

4.57 Where the LREC 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 LREC 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.

Delegation of the site-specific assessment to another body

4.58 The OREC Manager may make arrangements for SSAs relating to a particular site or sites to be delegated to another suitable local body. The terms of the delegation
should be set out in a written agreement, which should be approved by the Operations Director. 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.

4.59 The assessment body should have expertise in the management of health-related research and knowledge of the research site(s) and local researchers. In particular, the R&D Department of the local NHS Trust, Health Board or PCT, or a research consortium that provides care organisations with advice on research governance, would be a suitable body. Separate arrangements may need to be made for assessment of NHS and non-NHS sites.

4.60 The OREC Manager may also make special arrangements to establish a site assessment panel to conduct SSAs. The panel could be jointly composed of members of more than one LREC in the area, or of both LREC members and R&D staff. Other individuals with relevant expertise could be invited to join the panel.

4.61 The agreement between the OREC Manager and the assessor should include provision for the following:

- Definition of the research site(s) covered by the agreement.

- Procedures for referral of valid applications for SSA to the assessment body by the LREC Co-ordinator.

- All SSAs to be reviewed by at least two assessors, including an individual of appropriate seniority (such as the R&D Manager).

- Compliance with the guidance in paragraph 4.44 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 LREC Co-ordinator in writing within 25 days of the receipt of the valid application.
The LREC 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 LREC and the OREC Manager should be kept informed (see paragraph 4.69).

Monitoring of the agreement by the OREC Manager, with a formal review at least annually.

**Action by the main REC following site-specific assessment**

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

*No objection on site-specific grounds*

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

4.64 When giving a favourable ethical opinion for any study requiring SSA, the main REC should at the same time give specific approval for all sites for which notification of no objection has so far been received from the relevant LREC. This includes single-site studies where the SSA is carried out by the main REC alongside the ethical review. Approved sites should be listed on form SF1, which should be signed by the Chair (or by the Co-ordinator on behalf of the Chair) and enclosed with the letter to the Chief Investigator. A copy of the form should be sent to the sponsor. Where more than one sponsor has been named on the application, the form should be sent only to the sponsor nominated to take responsibility for communications with the REC. In the case of CTIMPs, a copy of the form should also be sent to the MHRA (see address at paragraph 3.63).

4.65 Where the main REC is not a LREC 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 LREC concerned or with the OREC Manager (see paragraph 4.53).

• There may have been a difference of view with the Chief Investigator about whether the study should be SSA-exempt, in which case the SSA process might have been initiated later than normal and more time needs to be allowed.

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 research site.) Form SF1 does not need to be sent at this point. As soon as one or more SSAs have been notified with no objection, SF1 should be raised and sent to the Chief Investigator with letter SL21.

4.66 It is the responsibility of the Chief Investigator to notify the Principal Investigator at each 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 care organisations.

4.67 Where, following the issue of a favourable ethical opinion, a further notification of no objection for a site is received from a LREC, the main REC should confirm the favourable opinion for the new site by issuing letter SL21 to the Chief Investigator, copied to the sponsor. An updated version of SF1 should be enclosed, adding the new site(s) to the list of sites with a favourable opinion. (In the case of studies given ethical approval prior to 1 March 2004, SL22 should be used in place of SL21. Only the new sites should be listed and there is no need to issue SF1.) In the case of CTIMPs, a copy of the letter should be sent to the MHRA. In the case of large studies with many sites, new versions of SF1 may be issued at intervals provided that the favourable opinion for any site is confirmed within 35 days of the date of receipt of a valid application for SSA by the LREC.
Objection on site-specific grounds

4.68 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 4.69 or 4.70 applies. The Chief Investigator should be advised of the reasons for an unfavourable opinion using SL23.

4.69 The main REC may contact the LREC (or delegated assessor) 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 relevant LREC and the OREC Manager with responsibility for the LREC should be notified in advance, and it may be helpful for the main REC to discuss the issues with the Chair of the LREC (or the delegated assessor) and explain the reasons for the decision.

4.70 If the LREC notifies the main REC of objections, and information is subsequently received from the Principal Investigator that resolves the issues causing concern, the LREC should contact the main REC as soon as possible to explain that the objections no longer apply. After any necessary discussion with the LREC, 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.

4.71 There may be cases where the objections from a site-specific assessor alert the main REC to the need to review the suitability of other sites. The main REC may write direct to relevant LRECs to explain the concerns that have arisen. LRECs may be asked to review the SSA, or some particular aspect of the SSA, and notify the main REC by a specified date if there are new objections.

Representations by the Chief Investigator

4.72 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 LREC as appropriate). The Chief Investigator should not be permitted to approach the LREC or other assessor directly.

Revision of the main application with implications for SSA

4.73 Where the Chief Investigator revises the main application during the ethical review, the information given to LRECs in Part C of the 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 based on the existing version of Part C. However, the Chief Investigator may be required to send an amended version of Part C for information only to LRECs that have already received applications for SSA, with a covering letter highlighting the changes. (Any LREC concerned about the implications of the changes for the suitability of the local site should notify the main REC.) Any new application for SSA submitted subsequently should be based on the amended Part C.

- Where the revisions are ethically acceptable but could have significant implications for the site-specific assessment, the Chief Investigator may be required to revise Part C and arrange submission of new applications for SSA. The SSA process should be re-started. Notifications already received from site-specific assessors will no longer be valid. The new Part Cs should be given a new SSA reference by LRECs. This option, which will delay the process of approving sites, should only be taken exceptionally where the existing version of Part C is clearly insufficient for adequate site-specific assessments to be made locally.

- In some cases (see paragraph 5.56), the revisions may be so fundamental that an unfavourable opinion should be given and a new application submitted including new versions of Part C.
Unfavourable opinion on the main application

4.74 Where the main REC issues an unfavourable opinion on the main application, RED will alert all LRECs that have received, or subsequently receive, applications for SSA. Any SSA that is underway should be discontinued.

Extension of the research to additional sites

4.75 Where, following the issue of a favourable ethical opinion, the sponsor(s) or Chief Investigator wishes to extend a single-site or multi-site research study to additional sites with Principal Investigators, the procedures in paragraph 5.62 should be followed. As and when the main REC receives further notifications of no objection, it should confirm the favourable opinion for the site by issuing SL21 together with an updated version of SF1.

4.76 In the case of SSA-exempt studies there is no requirement for the Chief Investigator or sponsor to notify the main REC of extension to additional sites in accordance with the protocol. Specific ethical approval for individual sites is not required in such studies. However, research governance approval should still be obtained from the R&D Departments for relevant care organisations before research procedures commence at any NHS site.

Appointment of a new Principal Investigator

4.77 Procedures for approving the appointment of a new Principal Investigator at a site are described in paragraph 5.62. When confirming the continuation of the favourable ethical opinion for the site, the Co-ordinator of the main REC should issue SL21 together with an updated version of SF1. A copy should be sent to the sponsor and, if applicable, the MHRA.

Closure of sites

4.78 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 Co-ordinator of the main REC should note the position on the current version of SF1. There is no requirement to issue a new version to the Chief Investigator and sponsor.

4.79 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

4.80 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.

4.81 Neither the main REC nor the LREC 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.

4.82 Where concerns are drawn to the attention of the LREC, it may review the original site-specific assessment or request further advice from a delegated assessor. The LREC or delegated assessor may seek further information from the Principal Investigator and/or request submission of a new Part C or CV if necessary. If it is not possible to resolve the concerns, the LREC should bring them to the attention of the main REC as soon as possible. The OREC Manager should be notified.

4.83 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 LREC.

Suspension or termination of ethical opinion for a site

4.84 A formal decision to suspend or terminate the ethical opinion for a research site may only be taken by the main REC. Procedures are set out in paragraphs 9.78-9.80.
**Adults with incapacity in Scotland**

4.85 Where the research participants include adults in Scotland who are physically or mentally unable to consent for themselves (see paragraphs 1.34-1.38), the SSA should be submitted to the relevant LREC in Scotland and processed in the normal way.

**Research governance approval by care organisations**

4.86 Research governance approval should be sought from the R&D Department for the relevant care organisation before any research procedures are commenced at a particular site. This applies to all research within the NHS. Although some research sites may be designated as SSA-exempt for the purposes of the ethical review, all investigators and local collaborators should seek approval to participate from the R&D Department. Where the investigator or collaborator does not hold a substantive contract with the care organisation, it may be necessary for an honorary contract to be issued in order to ensure that indemnity is provided.

4.87 It is the responsibility of the Chief Investigator for the study to advise local Principal Investigators or collaborators of the need to apply for research governance approval before commencing research procedures. The standard letters sent by the main REC should ensure that Chief Investigators are aware of their responsibilities in this respect.

4.88 RECs are not responsible for notifying R&D Departments of care organisations about proposed research or instigating research governance approval procedures (see paragraphs 3.61-3.62).

**Amendments to multi-site research**

4.89 Procedures for reviewing amendments to multi-site research are set out in Section 5, including extension to additional sites (paragraphs 5.62-5.63), appointment of new Principal Investigators (paragraphs 5.69-5.70) and site-specific protocol amendments (paragraphs 5.72-5.74).
Providing SSA to ethics committees outside the NHS

4.90 LRECs may occasionally receive applications for site-specific assessment relating to research under review by an ethics committee outside the NHS REC system. Some of these applications may relate to CTIMPs, in particular trials of gene therapy being reviewed by the Gene Therapy Advisory Committee (GTAC).

4.91 The LREC should generally agree to undertake SSA where requested. If in doubt, the Chair or Co-ordinator should seek advice from the OREC Manager or the Operations Director at COREC. The SSA should be processed in the normal way. Where RED cannot be used to notify the outcome of the SSA to the responsible ethics committee, SL19 should be used.
Section 5

Amendments to research given a favourable opinion

The EU Directive and 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.

The sponsor of a CTIMP must notify a substantial amendment both to the MHRA and the main REC. It may require both authorisation from the MHRA and a favourable opinion from the REC. In some cases one agency may be notified for information only. It is the sponsor's responsibility to decide what is substantial, though the REC may give advice if requested.

For other research, 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 amendment form. For other research the COREC form should be used. Reasons for the changes should be fully explained and amended documentation provided.

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 amendment may not be re-submitted.

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 LRECs.

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.
Section 5  Amendments to research given a favourable opinion

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 both to the MHRA and to 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
(d) 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. In some cases, the amendment may be for information only of one or other agency.

5.5 In the UK, all substantial amendments to CTIMPs will therefore be notified to both the MHRA and the main REC, but the sponsor will not always request an ethical opinion. Where no ethical opinion is requested, the REC is not required to review the amendment. Where the sponsor requests an ethical opinion, 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 Department of Health and the devolved administrations is that the statutory provisions relating to substantial amendments to CTIMPs should generally apply to the review of 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.

5.9 Substantial amendments should normally be reviewed at a meeting of a sub-committee of the REC, or where time allows by the Committee. They should not be reviewed by the Chair acting alone.
Revision of the application before the commencement of the research

5.10 A research study is considered to have commenced when the first patient gives written informed consent to participate. 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 would have been considered a “substantial amendment” after commencement of the study, then the same procedures apply as for review of substantial amendments.

Notices of amendment

5.11 For CTIMPs, the EU Notification of 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.

5.12 For all other research, the COREC Notice of Amendment form should be used. This is published on the COREC website and may be revised from time to time. The form may be submitted by either the sponsor or the Chief Investigator, but should always be signed by the Chief Investigator.

5.13 In all cases, the form should summarise the change(s) included in the amendment, and briefly explain the reasons in each case. One notice of amendment may refer to a number of different changes. The form should be completed in language comprehensible to a lay person.

5.14 The form should be accompanied by 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.

5.15 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.

5.16 Where a substantial amendment to a CTIMP requires authorisation by the MHRA but is sent to the main REC for information only, it is not necessary to include the supporting documentation provided to the MHRA.

5.17 The notice of amendment should be submitted only to the main REC and not to LRECs undertaking SSA.

5.18 The applicant should submit one paper copy of the notice of amendment form, with the appropriate signature in ink. One copy of the supporting documentation should be submitted either on paper or by e-mail, except where it includes a new version of the full protocol (in which case 4 paper copies should be sent). Additional photocopying of the amendment documentation for REC members is the responsibility of the REC office.

**Substantial amendments to CTIMPs – authorisation or ethical opinion?**

5.19 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 E, which has been agreed between COREC and the MHRA.

**Substantial amendments to CTIMPs notified for information only**

5.20 Where a substantial amendment to a CTIMP requires authorisation by the MHRA but is sent to the main REC for information only (for example, an amendment relating to the quality of the IMP), 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).

5.21 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 9.78-9.84). 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.

5.22 The MHRA will send the main REC a copy of its letter to the sponsor (or other person), giving a decision on the request for authorisation of the amendment. The letter should be placed on file. There is no need for the letter to be seen by the Chair or notified to the Committee.

Validation of notice of amendments

5.23 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 5.62.)

5.24 The relevant date (“the validation date”) is the working day on which the signed notice of amendment and all supporting documents are delivered to the address of the main REC, either in electronic or paper format. This applies whether or not the Co-ordinator or another member of the REC office staff is present to receive the documentation. Where packages are not date stamped on receipt, the date of receipt should be presumed to be the working day after the day of posting (1st class post) or the third working day after posting (2nd class post).

5.25 A notice of amendment should be accepted as valid if it meets all the following criteria:

(a) The relevant notice of amendment form has been completed.

(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 signed by the appropriate person.

5.26 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. (However, it is not necessary for the main REC to validate notices of amendment where an application for SSA is required – see paragraph 5.62.)

5.27 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 to the main REC. The Co-ordinator may offer to send on the documentation. The validation date will be the working day on which the main REC receives the documentation.

5.28 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. The Co-ordinator may however seek the advice of the Chair if, in the case of an amendment to a study other than a CTIMP, it appears that the amendment is not substantial and does not require ethical review (see paragraphs 5.31-5.34).

**Deciding whether an amendment is substantial**

*Clinical trials of investigational medicinal products*

5.29 For CTIMPs, the legal responsibility to decide whether an amendment is substantial lies with the sponsor. The Commission guidance (ENTR/CT1) includes guidelines on substantial amendments (see Annex D). While sponsors may be invited to take into account the guidance for RECs in paragraphs 5.33-5.34, it is a matter for them to decide whether to request an ethical opinion and/or authorisation from the competent authority.

5.30 Any amendment submitted by the sponsor on the EU Notification of Amendment form should be considered to be a substantial amendment and, if an ethical opinion has been requested, the main REC should review it. Equally, if the sponsor is satisfied that an amendment is not substantial, there is no legal requirement to notify either the
MHRA or the main REC. They may be notified to the main REC for information only by letter (see paragraph 5.36).

Other research

5.31 For research other than a CTIMP, the main REC has the discretion to decide whether or not a proposed amendment is substantial (as defined in paragraph 5.3) and requires ethical review. The Co-ordinator has the discretion to make this decision on behalf of the REC in straightforward cases. However, where the Co-ordinator is in any doubt about the designation of an amendment, he/she should invite the Chair to review the documents. Other members may be consulted where necessary, or exceptionally the documents may be considered at a meeting.

5.32 In making this judgement, 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.

5.33 The following changes should normally be regarded as substantial:

- Changes to the design or methodology of the study, or to background information affecting its scientific value
- Changes to the procedures undertaken by participants
- Any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study
- 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 key collaborator, or temporary arrangements to cover the absence of a CI

• A change to the insurance or indemnity arrangements for the study

• Inclusion of a new research site (not listed in the original application) in a study requiring SSA (see paragraph 5.62)

• Appointment of a new Principal Investigator at a research site (see paragraph 5.69)

• A significant change to the definition of a research site requiring SSA (see paragraph 5.71)

• A change to the “SSA-exempt” status of a study (see paragraph 4.23)

• A change to the definition of the end of the study (see paragraph 9.73)

• Any other significant change to the protocol or the terms of the REC application.

5.34 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:

• Correction of typographical errors in the protocol or other study documentation

• Other minor clarifications of the protocol

• Changes to the Chief Investigator’s research team (other than appointment of key collaborators)
Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator)

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

Inclusion of new sites in SSA-exempt studies (see paragraph 4.20)

Extension of the study beyond the period specified in the application form (see paragraph 9.10).

5.35 Changes to contact details for the sponsor (or the sponsor’s representative), Chief Investigator or other project staff are minor amendments but should be notified to the main REC for information. Changes to contact details for Principal Investigators should be notified both to the main REC and the relevant LREC.

Notification of minor amendments

5.36 Where changes are made to a research study that the sponsor (or Chief Investigator) 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 updating 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.

5.37 Minor amendments should be noted by the Chairman but 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).
5.38 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 and may suspend or terminate a favourable opinion if serious concerns arise (paragraph 9.78-9.84). 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.

5.39 Where the sponsor or Chief Investigator for a study other than a CTIMP submits a valid notice of amendment, but it appears that the changes described could be regarded as minor amendments, the Co-ordinator should write to the Chief Investigator using SL31, confirming that ethical review is not required. The letter should be sent within 35 days of receiving the notice of amendment. The changes may be implemented immediately, provided that they do not affect the research governance approval of the research given by the care organisation(s). It is the responsibility of the Chief Investigator (or Principal Investigators or local research collaborators in the case of a multi-site study) to inform the care organisation(s) if necessary.

**Requests for advice on whether an amendment is substantial**

5.40 If the sponsor or Chief Investigator seeks advice from the main REC about the designation of an amendment prior to submitting it, the Co-ordinator should proceed as follows:

- In the case of a CTIMP, it should be advised that this is a matter for the sponsor, although the guidance for RECs in paragraphs 5.33-5.34 may be voluntarily taken into account.

- In the case of any other research, the Co-ordinator may give advice on behalf of the REC, or refer the matter to the Chair. If in any doubt about the matter, the Chief Investigator should be required to submit a notice of amendment for review.
Review of substantial amendments

5.41 Except where paragraphs 5.45 or 5.48 apply, substantial amendments should be reviewed by a sub-committee of the relevant REC (see Section 6) or exceptionally 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 5.48).

5.42 The Chief Investigator may be invited to attend the sub-committee or Committee meeting to respond to questions about the amendment.

5.43 The decision reached at the meeting should normally be either a favourable or unfavourable opinion of the amendment. 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
SL33 Unfavourable opinion of substantial amendment

5.44 In the case of CTIMPs, the opinion letter should be copied for information to the MHRA (see address at paragraph 3.63). Where the MHRA has been asked to authorise a substantial amendment, it will send a copy of its letter of authorisation to the main REC for information.

5.45 Where a substantial amendment relates solely to the addition of a trial site or appointment of a new Principal Investigator (see paragraphs 5.62 and 5.69), the outcome of the SSA should be processed by the main REC in the normal way (see paragraphs 4.62-4.74). There is no requirement for the amendment to be formally reviewed at a meeting of the Committee or sub-committee of the main REC. Other amendments relating to individual trial sites should be reviewed by the main REC according to normal procedures.

Further information or clarification from the applicant

5.46 The 35 day clock does not stop pending receipt of any further information or clarification requested by the REC relating to a substantial amendment. The REC
should not, therefore, normally request further information prior to giving its opinion. Where the information supplied by the applicant is not sufficient to enable a favourable opinion to be given, the amendment should normally be rejected.

5.47 If time allows, however, the REC may invite the 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 should be rejected.

5.48 The applicant may be invited to submit a modified amendment taking account of the REC’s concerns. The members present at the meeting 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 paragraph 5.50-5.54.

5.49 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

5.50 Where the REC gives an unfavourable opinion of a substantial amendment, the 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.

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

5.52 The Co-ordinator should make arrangements for a modified amendment to be reviewed as soon as possible. It should be reviewed at a sub-committee meeting or, if authority has previously been delegated under paragraph 5.48, by the Chair. The REC should decide to 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). In the case of CTIMPs, the opinion letter should be copied for information to the MHRA (see address at paragraph 3.63).

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

5.54 Where an unfavourable opinion is given on a modified amendment, it may not be re-submitted.

**Appeals**

5.55 There is no provision for appeal against a decision of the main REC to give an unfavourable opinion of a substantial amendment.

**Amendments requiring submission of a new application**

5.56 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, the REC may give an unfavourable opinion and instead request submission of a new application for full ethical review. 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).
- Recruitment of a new type of participant (especially if these would be regarded as being from vulnerable groups).
5.57 Amendments involving the submission of a separate protocol should always require the submission of a new application.

Amendments to multi-site studies

5.58 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 5.62-5.74.)

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

5.60 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 5.56. It may well be that a new application is required for the study as a whole in such cases.

5.61 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 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 relevant LRECs 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 LRECs 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 LREC should consider any such request and respond in writing on behalf of the LREC. 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 LREC, the main REC may review the favourable opinion for a site at any time (see paragraph 9.78-9.84).

**Amendments relating to individual sites**

*Inclusion of new sites requiring SSA*

5.62 The inclusion of a new research site in a study requiring SSA should be treated as a substantial amendment, requiring confirmation of a favourable ethical opinion from the main REC. An opinion on the new site should be given by the main REC within 35 days. The following procedures apply:

- In all cases the Chief Investigator should arrange for the Principal Investigator to apply for SSA according to normal procedure.

- The LREC Co-ordinator should validate the application for SSA in the normal way. The main REC will be notified by RED that a valid application has been received.

- In the case of a CTIMP, the sponsor (or sponsor’s representative) should also send the European Commission notice of amendment form to the main REC, giving the name and address of the new site and Principal Investigator. *This*
additional requirement only applies where the site was not included in the list of proposed trial sites in the original REC application and request for authorisation to the MHRA (see paragraph 5.63). Sites already notified to the main REC and MHRA may be added by submitting SSA only.

- In the case of a non-CTIMP, there is no requirement for the Chief Investigator to submit a notice of amendment form to the main REC. All sites may be added by submitting SSA only.

- In all cases, the 35 day time period for the review begins when a valid application for SSA is received by the LREC. The outcome of the SSA should be notified to the main REC within 25 days of the receipt of the application.

- The main REC should issue the opinion for the new site within 35 days by issuing SL21 (with an updated version of SF1) or SL22. A copy should be sent to the sponsor and, in the case of a CTIMP, to the MHRA.

5.63 In the case of new sites in CTIMPs requiring a notice of amendment (see paragraph 5.62), the main REC should not issue the opinion until it has received both the notice of amendment form and the outcome of the SSA. It is the responsibility of the sponsor to ensure that these requirements are complied with. If only the outcome of the SSA is received by Day 35, the Co-ordinator may contact the sponsor to request that the notice of amendment be sent, but is not obliged to do so. When the notice of amendment is received, the opinion should be issued.

Exemption from SSA

5.64 In the case of studies designated as “SSA-exempt” (see paragraph 4.20), the inclusion of an additional site is not a substantial amendment and does not need to be notified to, or approved by, the main REC. It is sufficient for information on the number of sites taking part in the study to be included in the annual progress report.

5.65 If the study is “non-exempt” (see paragraph 4.20), an application for SSA should normally be submitted. However, if the new site(s) appears to meet the criteria for SSA exemption, the sponsor or Chief Investigator may write to the main REC
requesting that the site should be individually exempted from SSA (see paragraph 4.32).

Extension to additional domains

5.66 Where a research study (other than a CTIMP) is being conducted within one domain, and it is proposed to extend it to additional sites within one or more additional domains, the LREC that gave the favourable ethical opinion should continue as the main REC. (However, research that the Chief Investigator plans from the outset to conduct in two or more domains should be allocated through CAS initially in accordance with paragraph 1.19.)

5.67 Where a CTIMP with a favourable opinion from a Type 2 recognised REC (see paragraph 1.13) is to be extended to sites within one or more additional domain, a new application for ethical review should be submitted for review by a Type 3 recognised REC.

Adults with incapacity in Scotland

5.68 Special procedures apply to non-CTIMPs where the study involves adults with incapacity and it is proposed to extend the study to include research participants in Scotland for the first time. In such cases, there is a legal requirement for the research to be approved by “the Ethics Committee” constituted by Scottish Ministers under the Adults with Incapacity (Scotland) Act 2000 (see paragraph 1.37). As well as obtaining the site-specific assessment from the relevant LREC, the main REC for the study should formally obtain the written approval of the MREC for Scotland Committee A before extending its favourable ethical opinion to a site in Scotland. A copy of the approval from MREC for Scotland Committee A should be provided to the applicant with the favourable opinion letter.

Appointment of a new Principal Investigator at a site

5.69 The appointment of a new Principal Investigator at a site is a substantial amendment, requiring a favourable opinion from the main REC. A new Part C should be submitted for SSA and the procedures set out in paragraph 5.62 should be followed. The research should normally continue at the site pending re-confirmation of the
favourable opinion, unless the main REC has serious concerns about the safety or welfare of participants.

5.70 Other changes to the local research team at individual sites should not be regarded as substantial amendments. At the discretion of the Principal Investigator they may be notified to the relevant LREC by letter for information only. A notice of amendment form should not be used and it is not necessary to submit a new version of Part C.

Redefinition of research sites

5.71 A significant change to the definition of a research site in a study requiring SSA is a substantial amendment, requiring re-confirmation of the favourable opinion for the site(s) by the main REC. This could apply where, for example, one or more sites are to be combined into a consortium with a single Principal Investigator, or a site is to be divided into separate accountable units. A new Part C should be submitted for SSA and the procedures in paragraph 5.62 should be followed. The research should normally continue at the site pending re-confirmation of the favourable opinion, unless the main REC has serious concerns about the safety or welfare of participants.

Site-specific amendments to the protocol or information for participants

5.72 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 5.34), 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.

5.73 Where a site-specific amendment is substantial, a notice of 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 5.61.

5.74 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

5.75 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 at Part B Section 7 of the application form, signed by the new Chief Investigator.

5.76 If the new Chief Investigator will also be appointed as the local Principal Investigator at an individual research site, this should be made clear on the notice of amendment form. An amended version of Part C of the form and the CV should be sent to the relevant LREC, and SSA carried out in the normal way. The main REC should give opinions both on the appointment as Chief Investigator and the appointment as local Principal Investigator. SF1 should be revised and re-issued in the normal way.

Absence of Chief or Principal Investigator

5.77 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.
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. An application for SSA should be submitted and processed in the normal way.

- Where the absence is likely to exceed 4 weeks but will be less than 3 months, it may not be necessary to appoint an acting CI or PI but a letter may be sent to the main REC for information explaining what cover arrangements are being made. (In the case of an acting PI, the letter should be copied to the LREC and the care organisation. The LREC should notify the main REC if it has any concerns about the suitability of the arrangements.) 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 LREC.

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.

Urgent safety measures

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.
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:

- 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.

A sub-committee cannot undertake the primary review of a new application. This should always take place at a quorate meeting of the full Committee.

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.

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

Deputy members may attend 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.

Decisions of the sub-committee giving the ethical opinion of the REC, either confirming the Committee’s opinion on a new application or giving an opinion on an amendment, must always be made at an announced meeting. Meetings may take place either face-to-face or over the telephone (using conference facilities where possible). Other committee business, for example SSAs or reviewing progress reports, can be conducted in correspondence.

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 the meeting.
- Minutes of telephone meetings should be taken by the Chair if the Co-ordinator cannot follow the discussion using conference facilities.
- Decisions taken at a sub-committee meeting should be reported to the full Committee in the Co-ordinator’s report, or the minutes may be attached to the report.
Section 6  Sub-committees

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 COREC 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) Consideration of further information or clarification provided by applicants, (including any revisions of the application documentation); consideration of further advice from referees; and confirmation of the ethical opinion of the REC (see Section 3).

(ii) Review of notices of 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 quarterly or annual safety reports together with lists of SUSARs or 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 (see Section 4).
6.4 A sub-committee should not undertake the primary review of a new application for ethical review. Applications should be considered at a quorate meeting of the full Committee prior to any further consideration by a sub-committee.

6.5 Decisions of a sub-committee to confirm the ethical opinion of the REC on an application, or to give an ethical opinion on a substantial amendment, should be made at either a face-to-face or telephone meeting. Other sub-committee business may be conducted by correspondence between the members (see paragraph 6.17).

Authority of sub-committees

6.6 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

6.7 A decision to establish a sub-committee should be taken at a meeting of the REC.

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

(i) A standing sub-committee may be established. This should consist of at least two 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. Other members may be invited to contribute to standing sub-committee business as appropriate.

(ii) 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 or vice-Chair (or, if neither is available, the alternate vice-Chair) should be present at all meetings.

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 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

6.11 The quorum for any meeting of a sub-committee is at least the Chair or vice-Chair (or, if neither is available, the alternate vice-Chair) and at least one other member. The Chair and vice-Chair together constitute a quorum. The Chair is responsible for ensuring that appropriate expertise is available, depending on the business for the meeting. It is desirable but not essential for a lay member to be present.

Distribution of papers

6.12 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

6.13 It is recommended that face-to-face meetings take place where practicable. However, sub-committee meetings may be conducted over the telephone. Where available, teleconferencing facilities should be used. If such facilities are not available, it is acceptable for business to be conducted over a normal telephone line between the Chair and one other member.

6.14 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.

Submission of written comments prior to meetings

6.15 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.

6.16 A member who submits written comments but does not attend the meeting either in person or on the telephone does not count towards the quorum.

Conduct of sub-committee business by correspondence

6.17 Sub-committee business may be conducted by correspondence, including e-mail, except as specified in paragraph 6.5.

6.18 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. 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.

6.19 Matters considered by correspondence should be recorded in the Co-ordinator’s next report for the REC (see paragraphs 2.15-2.20).

Attendance of investigators

6.20 The REC may invite the Chief Investigator or the local Principal Investigator for a research study to attend a sub-committee meeting where matters relating to the study are to be discussed.
Co-opted members

6.21 A REC may co-opt one additional member at any sub-committee meeting. 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 2.41-2.42).

Referees

6.22 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 2.47(iii) should be followed.

Observers

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

Responsibilities of the Co-ordinator

6.24 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.

6.25 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) Keeping records of all comments submitted by members.

Minutes of sub-committee meetings

6.26 The requirements of paragraphs 2.75-2.77 apply to the minutes of sub-committee meetings in the same way as for REC meetings.

6.27 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.

6.28 The minutes of sub-committee meetings are confidential, and paragraph 2.79 applies in the same way as for REC meetings.

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

Summary

There are two options available to an applicant who has received an unfavourable opinion: submission of a new application; or appeal against the unfavourable opinion.

Both new applications and appeals are given a new REC reference number on 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, new Part Cs 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 Operations Director in consultation with the Chair and OREC Manager 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 COREC and the same system of appeal applies to CTIMPs and other research.

Notice of appeal should be sent in writing to the OREC Manager (if it is a locally allocated application) or to the Operations Director at COREC (if it is an application allocated through CAS). The notice must be sent within 90 days of the previous opinion. Appeals will normally be allowed though COREC 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 OREC manager or Operations Director 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.
Section 7 Further review of research given an unfavourable opinion

Options available to the applicant

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

(i) He/she may submit another application, which should be reviewed as a new application.

(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”).

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 (at A55) 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 OREC 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, new applications for SSA should be submitted by Principal Investigators and processed by LRECs 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.

Applications submitted direct to LRECs

7.6 In the case of applications submitted direct to LRECs, the applicant should book the application in the usual way with a LREC within the domain. It is highly desirable that the new application is 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 LREC within the domain if he/she prefers.

7.7 The Co-ordinator of the first LREC should offer the applicant the option of submitting to another LREC in the domain (or if necessary another domain within the OREC area) where there is a significant risk that the first LREC 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 LREC’s next closing date
- The agenda for the next meeting of the LREC is full
- The next meeting of the LREC will need to be cancelled due to a risk that it may not be attended by sufficient members.

Similarly, if the applicant submits the application direct to the first LREC without prior booking, the Co-ordinator may offer the applicant the option of transferring it in these circumstances.

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

Applications allocated through CAS

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, 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 OREC Manager based on the
(ii) The OREC 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 OREC Manager considers that the criteria in paragraph 7.12 apply, a recommendation should be made to the Operations Director at COREC to declare the applicant vexatious.

(iv) If the Operations Director endorses the recommendation, 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 Operations Director.

(v) The Operations Director should inform the applicant in writing that any further correspondence or new applications should be sent direct to the Operations Director.

(vi) On receipt of any further correspondence or a new application, the Operations Director 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 UKEGA may extend this period in a particular case. UKEGA 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” (MREC for Scotland Committee A) under the Adults with Incapacity (Scotland) Act 2000.

7.16 The policy of the Department of Health and the devolved administrations is that COREC should exercise the functions of UKEGA relating to appeals. The procedures for appeals should apply to any research reviewed by a REC in the UK, except where paragraph 7.15 applies.

Notice of intention to appeal

7.17 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.

7.18 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 COREC reserves the right to disallow an appeal.

7.19 In the case of any application allocated through the Central Allocation System, notice should be given by the applicant in writing to the Operations Director at COREC. The Operations Director should then allocate the application to another recognised REC for review, taking into account geographical proximity to the Chief Investigator’s professional base, and book an agenda slot at its next meeting through CAS.
7.20 In the case of applications made locally, notice should be given in writing to the relevant OREC Manager, who should normally allocate the application to another LREC within his/her area of responsibility and arrange for an agenda slot to be booked at the next meeting.

7.21 The Operations Director at COREC, or the OREC 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 applicant should be notified whether or not the appeal is allowed using SL36, which should be sent by the Operations Director or the OREC Manager as appropriate. Where the appeal is allowed, the letter should state which REC has been allocated to review the application, the date of the meeting at which it has been booked and the closing date for submission. Copies should be sent to the Co-ordinators of both RECs. Where the appeal is disallowed, a letter should be sent to the Chief Investigator giving reasons.

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

**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 The application should be re-entered on RED as if it were a new application, so that it can then be processed on RED in the normal way. The applicant should be advised
of the new reference number. There is no requirement for the normal validation letter to be sent.

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.

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 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.

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.
Section 8: Expedited review

Summary

A REC has a total of 60 days to give an opinion on any valid application received. There is no statutory provision for expedited review. Co-ordinators and Chairs of RECs have no authority to expedite the usual procedure for ethical review.

In very exceptional circumstances, however, there may be a need to start a research project urgently for reasons of public policy, for example:

- A research field causing public anxiety
- An urgent threat to public health
- A unique opportunity for research that is likely to be temporary.

In these circumstances, the sponsor and/or Chief Investigator should contact the Director of COREC directly for advice. The Director of COREC will consult with UKECA and Ministers as necessary and, if appropriate, will authorise an expedited review.

If permission is given for expedited review, the sponsor or Chief Investigator should submit the standard COREC application form with all the usual documentation. The Operations Director at COREC will arrange for the application to be validated on the day of receipt.

COREC will allocate the application for review in one of the following ways:

- An existing REC may be appointed to review the application. Two members with relevant expertise could be co-opted from other RECs, and/or relevant experts may be specially appointed as members for review of this application.

- A new REC may be established for the review of the application. If it is a CTIMP, the REC will need to be legally recognised by UKECA.

The “appointed REC” should follow SOPs during review, except that COREC will specify the time periods required for processing the application.

Procedures for site-specific assessment by other RECs may be waived, but the Chief Investigator or sponsor should provide the appointed REC with evidence that the local sites, facilities and investigators involved are adequate. The appointed REC may consult relevant LRECs or care organisations directly for advice.

If a specially appointed REC issues a favourable opinion and is later abolished, COREC should re-assign monitoring and reviewing responsibilities to another recognised REC.
Section 8 Expedited 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 days, which may be suspended once pending receipt of further information from the applicant.

8.2 There may however be wholly 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 health-related research study to commence as quickly as possible. Such circumstances could include the urgent need for research data in a field that is currently the subject of major public anxiety, or where there is an urgent threat to public health. There could also be a need to capitalise on a unique opportunity for significant research that is likely to prove temporary.

8.3 Where a research sponsor or Chief Investigator believes that such circumstances may apply, he/she should contact the Operations Director at COREC directly for advice. The Co-ordinators or Chairs of individual RECs have no authority to expedite the normal procedures for ethical review.

8.4 Where, after consultation with UKECA and Ministers as necessary, the Operations Director considers that the circumstances justify it, the sponsor or Chief Investigator may be given permission to submit an application for expedited review.

Procedures for expedited review

8.5 An application for expedited review may be submitted by either the sponsor or the Chief Investigator of the proposed research. The standard COREC application form should be used and all the usual supporting documentation should be provided. The application should be submitted to the Operations Director at COREC. A decision on validation should be made on the day of receipt and notified to the applicant.
8.6 The Operations Director should then allocate the application for review in one of the following ways:

(i) An existing REC may be appointed to review the application. COREC 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 COREC 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 COREC but should include both lay members and relevant experts. A Chair and Co-ordinator should be appointed by COREC.

8.7 The REC appointed to review the application (“the appointed REC”) should do so following standard operating procedures, except that COREC may specify the time periods within which each stage of the process should be completed.

8.8 Where the application relates to a multi-site research study with Principal Investigators, the appointed REC is responsible for giving ethical approval for each site as part of a favourable ethical opinion, but the normal procedures for site-specific assessment may be waived at the discretion of COREC. 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 Part C of the application form is completed for each proposed 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 LRECs or care organisations for advice by telephone, e-mail or fax.

8.9 Where a favourable ethical opinion is given by a specially appointed REC under paragraph 8.6(ii), and that REC is later abolished, COREC should re-assign the responsibilities for monitoring the research and reviewing amendments to another REC.
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 months the Chief Investigator should give an explanation of the delay in the annual progress report. The Chair may allow a further 12 month period.

Progress reports on all studies should be sent to the main REC annually by the Chief Investigator using the COREC 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, including a global line listing and a safety assessment. Quarterly reports should also be provided where the sponsor is conducting trials of the product outside the UK.

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

The main REC is not required to review expedited reports of SUSARs. Quarterly and annual safety reports 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 COREC.

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 significant protocol “violation” or breach of 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 COREC form.

The main REC may review the ethical opinion at any time. Guidance is given on circumstances that might justify suspension or termination of the favourable opinion. Such a decision should be taken at a full Committee meeting.

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 OREC Manager and its appointing authority. The REC should not undertake its own investigations.
Section 9 Monitoring of research given a favourable opinion

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 COREC 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 COREC to request that a single main REC is appointed to take responsibility for monitoring of the research (see paragraph 10.10).

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, those LRECs responsible for site-specific assessment have no responsibility for proactive monitoring of the local conduct of the research.
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 relevant LREC or its sub-committee to discuss any new concerns relating to the suitability of the site.

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). It is open to the Chair to allow a further period of 12 months within which the trial should commence.

9.8 Should the project not commence within 24 months, the matter should be discussed at a meeting of the REC. At the discretion of the REC, the favourable ethical opinion may be terminated and the Chief Investigator required to submit a new application once the problems relating to the delay of the study have been fully addressed. Alternatively, a further period may be allowed.

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) using the appropriate form for declaring the conclusion or early termination of the study (see paragraphs 9.62-9.63). If a study is abandoned and it is later proposed to start it afresh, a new application should be made.

Duration of a favourable ethical opinion

9.10 The favourable ethical opinion of the main REC applies for the duration of the research, except where action is taken to suspend or terminate the opinion (see paragraph 9.78-9.84). Where the duration of the study is to be extended beyond the
period specified in the application form, the main REC should be notified for information by letter, giving reasons for the extra time needed to complete the research. (Annual progress reports should continue to be submitted if the study duration is extended in this way – see paragraphs 9.10-9.19.) 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 extension of follow-up. It is not necessary to obtain formal approval for extension of the study period, though the main REC may review its favourable opinion of the study at any time (see paragraph 9.78-9.84).

Progress reports

9.11 Progress reports on all research with a favourable opinion should be submitted to the main REC at least annually. The first annual report should be submitted 12 months after the date on which the favourable ethical 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.

9.12 When giving a favourable opinion on an application, the main REC may require as an approval condition that more regular reports should be submitted, or it may request an additional progress report at any time.

9.13 Progress reports should be in the format prescribed by COREC 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. Where it is proposed to suspend or terminate the REC’s favourable ethical opinion, the matter should be considered at a meeting of the REC (see paragraph 9.81).

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. Where it is proposed to suspend the REC’s favourable ethical opinion, the matter should be considered at a meeting of the REC (see paragraph 9.81).

9.18 In the case of multi-site studies, there is no requirement for copies of progress reports to be sent to relevant LRECs by the sponsor or Chief Investigator. Nor is there any requirement for local Principal Investigators to submit progress reports on the local conduct of the research to the relevant LREC, unless exceptionally the LREC considers this is necessary to monitor local issues relating to the suitability of the site.

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 COREC 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 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 LREC 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” (ENTR/CT3). The guidance describes the requirements to be followed by sponsors for safety reporting both to the competent authority and the ethics committee in each member state. This document is the main source of guidance for sponsors of CTIMPs in the UK. The following paragraphs summarise the key requirements.

Expeditated reporting of individual SUSARs in the UK

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 periodic line listings (see paragraphs 9.38-9.41). 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 In addition, for IMPs without a marketing authorisation in any Member State, other SUSARs associated with the IMP are subject to expedited reporting. This includes SUSARs occurring in another trial conducted by the same sponsor, or which come to the attention of the sponsor from another source. The main REC will only receive such reports where the SUSAR occurs in the UK.

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.

9.28 An adverse reaction is considered to be “unexpected” if its nature and severity are not consistent with the information about the medicinal product set out in the trial documentation.

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. Any additional relevant information must be reported within 8 days of sending the first report.

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.

9.31 An adverse event associated with placebo will not normally satisfy the criteria for a SUSAR. If this occurred exceptionally it should be reported.

9.32 Sponsors must also report to all investigators concerned any findings that could adversely affect the safety of study subjects. It may do so by means of periodic line listings of SUSARs, accompanied by a summary of the evolving safety profile.
9.33 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. (See paragraph 10.10 for guidance on the designation of the main REC in trials approved by ethics committees prior to 1 May 2004.)

Other expedited safety reports

9.34 The European Commission guidance recommends that expedited reports on the following occurrences should also be sent to the competent authority and the main REC according to the same timelines as SUSARs:

(a) single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. death)

(b) an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important

(c) post-study SUSARs that occur after the patient has completed a trial

(d) 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
- 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).

9.35 The sponsor should also keep the main REC informed of any significant findings and recommendations by an independent Data Monitoring Committee or equivalent body established for the trial.

9.36 It is not generally required to notify serious adverse events occurring in the trial not meeting the criteria for SUSARs, other than under paragraph 9.34(d) above.
Unblinding of reports

9.37 In the case of double-blinded trials, the European Commission guidance recommends that reports of SUSARs should normally be unblinded. So far as the UK is concerned, both the MHRA and the main REC will expect all such reports to be unblinded.

Periodic safety reports

9.38 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. Annual reports should 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. Although not a statutory requirement, it may be helpful to provide the REC with a cumulative line listing since the start of the trial.

9.39 Where the sponsor is conducting the trial or any other trials of the IMP outside the UK, it should also provide the main REC with quarterly safety reports (see paragraph 6.3.1.6.5 of ENTR/CT3). Quarterly reports should include a global line listing of all SUSARs occurring in relevant trials during the reporting period, together with an assessment of the safety of participants. This reporting mechanism meets the obligations of the sponsor under the Directive to report non-UK SUSARs to the ethics committee.

9.40 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 9.48).

9.41 Periodic 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.
Reporting timeframe for periodic reports

9.42 The reporting timeframe for periodic reports 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.

9.43 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).

9.44 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.

9.45 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.

Format of safety reports

9.46 Sponsors may adopt their own format both for expedited reports and periodic safety reports provided that the basic information set out in the European Commission guidance is included. Reports of SUSARs will normally be in the CIOMS-1 format (available at http://www.cioms.ch) that is widely accepted as the standard within the pharmaceutical industry. The required data elements for SUSAR reports and line listings are set out respectively in Annexes 3 and 4 to ENTR/CT3.

Submission of safety reports

9.47 Expedited and quarterly/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. Initial notifications of SUSARs may be made by fax, e-mail or telephone. Follow-up reports and all other safety reports should be sent to the REC office by post. Three copies should be provided of all enclosures, except for SUSAR reports (one copy only).
9.48 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 COREC website. The form should be signed in ink. 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.

9.49 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

9.50 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 to advise on safety issues. 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.

9.51 Sponsors are required to submit complete data on all SUSARs occurring in EU member states to the Eudravigilance CT module of the European Clinical Trials Database (EudraCT), as well as other specified safety data. 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 EudraCT. Where the MHRA raises safety concerns with the sponsor, it will directly inform the main REC so that any implications for the favourable ethical opinion can be addressed in parallel.
9.52 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.

9.53 The main REC should therefore review safety reports in accordance with the following guidance.

Review of safety reports by the main REC

9.54 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.

9.55 Quarterly and annual safety reports will be more helpful to the REC because they will contain complete line listings of SUSARs in the trial worldwide and an analysis of the data. All such 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 purpose of the review is to:

- Check the continued safety of the trial
- Check the accuracy of the risk/benefit analysis as described in the patient information sheet
- Consider the possible need for new information to be given to patients and their consent sought to continue in the study.
9.56 Where substantial 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 MHRA (see address at paragraph 3.63). The Chief Investigator may be requested to attend a meeting of the sub-committee or Committee to discuss the concerns of the REC.

9.57 Copies of the reports of Data Monitoring Committees should also be forwarded to the main REC. Such reports should be reviewed in the same way as quarterly and annual safety reports.

9.58 The Committee should be notified in the Co-ordinator’s report (see paragraph 2.15) of the receipt of quarterly or annual safety reports and copies of reports by Data Monitoring Committees. The report should state who has reviewed the safety reports, 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.

Safety reporting for other research

9.59 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.

9.60 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.
9.61 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 COREC website.

9.62 The Chief Investigator should include a report on the safety of participants in the annual progress report.

9.63 Individual reports of SAEs should be reviewed at a sub-committee or Committee meeting.

9.64 There is no requirement to provide reports to RECs other than the main REC.

**Protocol deviations and violations**

9.65 It is generally considered acceptable for a sponsor or Chief Investigator to make (or permit other investigators to make) minor deviations from a protocol to deal with unforeseen circumstances. Such deviations 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 promptly reported to the main REC. 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).

9.66 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 (see Section 5).

9.67 A distinction should be made between “protocol deviations”, which are agreed with the sponsor or 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.

9.68 The main REC should be notified of any significant protocol violation or significant breach of Good Clinical Practice (GCP) that raises serious concerns about the suitability of a site or investigator, the safety of participants or the validity of the
research data. Where this applies, the sponsor or Chief Investigator should notify the main REC as soon as the matter comes to their attention. The report of the violation should give details of when it 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 violation or breach of GCP should be considered at a meeting of the Committee or sub-committee. Where consideration is given to suspending or terminating the opinion, either for the whole of the UK or at an individual site, the REC should follow the guidance in paragraphs 9.78-9.84. Where fraud or misconduct is suspected, the REC should follow the guidance in paragraphs 9.89-9.91.

9.69 Where information about a significant protocol violation or significant breach of GCP comes to the attention of the LREC for a research site, this should be reported to the main REC.

9.70 There is no requirement to notify minor protocol violations or breaches of GCP not meeting the criteria in paragraph 9.68.

**Declaration of the conclusion or early termination of the research**

9.71 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 research.

9.72 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.

9.73 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. In most cases it will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol.

9.74 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).

9.75 The policy from COREC 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 COREC and published on the website.

9.76 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.

9.77 In general there is no requirement to submit an annual safety report or annual progress report with a declaration of conclusion or early termination. However, in the case of research lasting less than 12 months the REC has the discretion to request a final safety report.

Review of a favourable ethical opinion

9.78 The main REC may review its favourable ethical opinion of a study at any time. In particular, this might be prompted by safety reports, progress reports or any other information received about the conduct of the study. 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.

9.79 A favourable ethical opinion may be suspended or terminated by the main REC due to serious concern about one of the following:

(a) The scientific validity of the study
(b) The health or safety of participants
(c) The competence or conduct of the investigator(s)
(d) Serious or repeated breach of approval conditions
(e) A delay of at least 2 years in the commencement of the study
(f) The adequacy of the site or facilities
(g) Suspension or termination of regulatory approval for the study.

9.80 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 (see paragraph 4.84). The favourable opinion could continue to apply to other trial sites in these circumstances.

9.81 A decision by the REC to suspend or terminate a favourable ethical opinion should be taken only at a quorate meeting of the full Committee. Before taking this course the REC should weigh carefully the implications for any research participants already recruited. The Chief Investigator should be notified of the decision by the Chair using SL42. 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
- any action necessary to inform patients or arrange for their continuing treatment outside the trial protocol

_and, in the case of suspension,

- any conditions which are to be satisfied before the favourable opinion may be re-confirmed, either generally or at a particular site.

9.82 A copy of the letter should be sent to the sponsor and, in the case of single-site studies, the care organisation. In the case of a multi-site study, it is the responsibility of the Chief Investigator or the sponsor to ensure that other investigators, local collaborators and care organisations are informed. Where the opinion is suspended or terminated at a particular site, a copy of the letter should be sent to the Chair of the relevant LREC, and the action taken in relation to the site should be noted on form SF1.
9.83 In the case of a CTIMP, the Chair should write to the MHRA (see address at paragraph 3.63), explaining the action taken and inviting the Agency to consider suspending or terminating the Clinical Trial Authorisation.

9.84 The MHRA will directly inform the main REC where it suspends or terminates a Clinical Trial Authorisation (which will automatically halt the trial), and also where it reinstates 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.

Further reporting after the conclusion of the trial

9.85 If after the conclusion or early termination of a trial 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

9.86 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. 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.

9.87 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.
9.88 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).

9.89 Where a REC receives information suggesting that any kind of fraud or misconduct 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 OREC Manager in writing, copied to the REC’s appointing authority. If the REC concerned is not the main REC for the study, a copy should also be sent to the main REC. It will be for the OREC Manager, in consultation as appropriate with the Operations Director at COREC and the appointing authority, to decide whether the information should be shared with other bodies so that the matter can be formally investigated. The OREC Manager should consider notifying the following:

- The research sponsor
- The R&D Department for any relevant NHS care organisation(s)
- MHRA GCP Inspection Unit *(CTIMPs only – see paragraph 9.95)*
- MHRA (Devices) *(clinical investigations of medical devices only).*

The Operations Director, the appointing authority and the reporting REC should be kept fully informed.

9.90 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 paragraph 9.78-9.84). The opinion 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.

9.91 A member of a REC who becomes aware of possible fraud or misconduct in research should report this to the Chair and Co-ordinator of the REC, who will be responsible for reporting the matter in accordance with paragraph 9.89.
Criminal offences

9.92 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.

9.93 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.

9.94 Where a REC receives information suggesting that a criminal offence may have been committed, it should proceed as in paragraph 9.89.

GCP inspections

9.95 Good Clinical Practice (GCP) guidelines and regulations provide a standard for the conduct of clinical trials. 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 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.

9.96 Inspections are carried out to protect the public (both current and future patients), to meet legal obligations and enforce applicable legislation, to provide assurance of compliance with GCP guidelines and regulations, to detect and take action relating to serious GCP 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.
9.97 Serious concerns about GCP compliance issues should be drawn to the attention of the OREC Manager and appointing authority under the procedures for notifying possible fraud or misconduct (see paragraph 9.89). Where appropriate, the OREC Manager should notify the inspectors by writing to the following address:

Operations Manager for GCP
MHRA Inspection & Standards Division
Market Towers
1 Nine Elms Lane
Vauxhall
London SW8 5NQ

Co-operation with inspections and investigations

9.98 The REC should co-operate fully if asked to assist with GCP inspections or criminal investigations. The OREC Manager and appointing authority should be kept informed.

9.99 Requests to provide information or assistance in connection with investigations by other bodies into suspected fraud or misconduct should be referred initially to the OREC Manager for discussion as appropriate with the Operations Director and appointing authority. With the permission of the OREC Manager, the REC should co-operate fully. The REC should not under any circumstances undertake its own investigations.
Section 10: Transitional arrangements

Summary

The EU Directive and the Clinical Trials Regulations came into force in the UK on 1 May 2004. This section gives guidance on ongoing review by the “main REC” of studies that received ethical approval before 1 May 2004. The transitional provisions for CTIMPs are set out in the Clinical Trials Regulations and have statutory force.

“Ongoing review” means all responsibilities of the main REC following approval. This includes ethical review of substantial amendments, approval of new sites and PIs, review of progress and safety reports, and all other monitoring responsibilities.

Transitional arrangements depend on whether:

(i) The study is a CTIMP or non-CTIMP.

(ii) The REC is recognised to review the study by UKECA (in the case of a CTIMP).

(iii) The study is single- or multi-site.

The guidance covers each scenario in detail. Key points are as follows:

- An ethical opinion given to a CTIMP by a REC that is recognised for the relevant type of trial remains valid until the conclusion of the trial. The REC continues as the main REC.

- An ethical opinion given to a CTIMP by a REC that is not recognised remains valid until 1 May 2006. The REC can undertake all responsibilities of the main REC until this date. At this point the opinion ceases to be valid, but in the meantime the sponsor may apply to a recognised REC for a new opinion. Guidance is given on the procedures for new applications. If the second REC gives a favourable opinion, it takes over as main REC.

- For non-CTIMPs with ethical approval from one LREC, this REC continues as the main REC. This applies whether or not the study is extended to sites in other domains.

- All multi-site studies previously approved by MRECs continue with the MREC as main REC. LRECs that gave “locality approval” - under Annex D of the previous MREC application form - continue as site-specific assessors but have no other responsibilities.

- Where a multi-site study was ethically reviewed and approved by more than one LREC, a single REC must be appointed by COREC as the main REC before any further decisions can be taken on the study. Normally this will be one of the LRECs that approved the study. If it is a CTIMP, the REC should be recognised.

Guidance is given on re-designating studies as SSA-exempt under the new SOPs.

Guidance is also given on transfer of responsibilities where a REC ceases to function following abolition or merger, or has its recognition revoked. OREC Managers are responsible for arranging for another REC to take over as main REC for outstanding applications and existing studies.
Section 10 Transitional arrangements

Introduction

10.1 This section gives guidance on the transitional arrangements applicable to:

- Ongoing ethical review of studies that received a favourable ethical opinion before 1 May 2004, i.e. responsibility for amendments, new sites and monitoring; and procedures for submission of fresh applications where legally required.

- Transfer of studies from a REC that ceases operation or has its recognition revoked, including both outstanding applications and ongoing ethical review of studies.

10.2 Applicants and REC Co-ordinators should contact OREC Managers wherever necessary for further advice on the interpretation of these procedures.

Studies with a favourable ethical opinion given before 1 May 2004

10.3 In this section all references to “favourable ethical opinion” include ethical approvals given by any duly constituted NHS REC prior to 1 May 2004. They do not apply to “locality approvals” given by LRECs under the procedures for multi-centre studies prior to 1 March 2004.

Single-site CTIMPs

10.4 Where the favourable ethical opinion was given by a REC that is now recognised by UKECA for the appropriate type of research, the opinion remains legally valid until the conclusion of the research. Except where paragraph 10.8 applies, the REC will continue as the main REC for all purposes, including the review of substantial amendments, approval of new sites and monitoring. Where it is proposed to add new sites, other LRECs will be responsible for site-specific assessment in the normal way.
10.5 Where the favourable ethical opinion was given by a REC that is not recognised by UKECA, or is not recognised for the appropriate type of research, the opinion remains legally valid until 1 May 2006. At this point, the opinion becomes invalid unless the sponsor or Chief Investigator has taken steps to obtain a favourable opinion from a recognised REC under paragraph 10.7.

10.6 A non-recognised REC, or a REC that is not recognised for the appropriate type of research, may therefore legally continue as the main REC for a CTIMP until 1 May 2006. Until this date it may give an opinion on a substantial amendment or the addition of a new site, receive progress reports and carry out other monitoring functions.

10.7 Where a CTIMP is still in progress after 1 September 2004 without a favourable opinion from a recognised REC or a REC that is recognised for the appropriate type of research, the Chief Investigator may submit a new application. The following guidance applies:

(i) The application should be booked through CAS in the normal way for ethical review by a REC that is recognised to review the research (“the second REC”).

(ii) The Co-ordinator of the second REC may contact the Co-ordinator of the REC that previously gave a favourable opinion (“the first REC”) and request a copy of all previous correspondence on the study. At the discretion of the Chair of the second REC, relevant correspondence on the previous application may be copied to members with the new application.

(iii) If a favourable opinion is given, this supersedes the opinion of the first REC and remains valid until the conclusion of the study, and the second REC will continue as the main REC.

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1 Where an ethics committee ceased to exist and all its functions were transferred to another ethics committee prior to 1 May 2004, and this committee is then recognised, all the ethical opinions of the former committees are treated as having been given by a recognised committee in accordance with paragraph 10.4. This applies particularly to the opinions given under the previous ethics committee system in Northern Ireland.
(iv) If an unfavourable opinion is given, the study may continue under the previously approved protocol until 1 May 2006, and the first REC continues as the main REC.

(v) The correspondence on the second application should be copied to the first REC for information.

10.8 Where the CTIMP has ethical approval from a Type 2 recognised REC, this REC may continue as the main REC except that its authority to give an opinion on research sites in another domain(s) would expire on 1 May 2006. At this point the Chief Investigator would be required to submit a new application for review by a Type 3 REC if proposing to extend the trial to become multi-domain.

Multi-site CTIMPs

10.9 Where the favourable ethical opinion was given by a MREC, paragraph 10.4 applies.

10.10 Where favourable ethical opinions were given by more than one LREC, these opinions remain valid. However, no further opinions should be given in relation to the study, in particular on substantial amendments or new sites, until one of the LRECs has been appointed by COREC as the main REC. The sponsor or Chief Investigator for any such study should apply as soon as possible in writing to the Operations Director at COREC, giving the following information:

- Full title of study
- Details of the Chief Investigator
- Names and references of the LRECs that gave a favourable opinion.

10.11 The application may indicate which of the LRECs the sponsor or Chief Investigator would prefer to be appointed as the main REC. The primary criterion should be that the LREC is recognised to review the appropriate type of research. The secondary criterion is geographical proximity to the Chief Investigator’s professional base.

10.12 COREC should appoint the main REC by writing to the sponsor or Chief Investigator, copied to all the LRECs concerned. The LRECs not appointed as main REC continue
to be responsible for any advice required by the main REC on issues relating to their own sites.

10.13 Where none of the LRECs concerned are recognised to review the appropriate type of research, the Operations Director should nevertheless appoint one of the LRECs as the main REC for the study. The sponsor and Chief Investigator should be made aware that the favourable opinion only remains valid until 1 May 2006 unless steps are taken to obtain a favourable opinion from a recognised REC under paragraph 10.7.

**Single-site non-CTIMPs**

10.14 The favourable opinion remains valid for the duration of the study and the LREC concerned should continue to carry out all the functions of the main REC, including the review of substantial amendments, approval of new sites and monitoring.

10.15 Where the Chief Investigator proposes to extend the study to another site, whether in the same domain or another domain, the LREC should continue as main REC. If the study involves procedures requiring SSA, this should be carried out in the normal way.

**Multi-site non-CTIMPs**

10.16 Where the favourable ethical opinion was given by a MREC, the opinion remains valid. The MREC will continue as the main REC for all purposes, including the review of substantial amendments, approval of new sites and monitoring. Where it is proposed to add new sites requiring SSA, other LRECs will be responsible for site-specific assessment in the normal way.

10.17 Where favourable ethical opinions were given by more than one LREC, these opinions remain valid. However, no further opinions should be given in relation to the study, in particular on substantial amendments or new sites, until one of the LRECs has been appointed by COREC as the main REC. The procedures in paragraphs 10.10–10.13 apply.
Previous “locality approval” for multi-site studies

10.18 Issues arise in relation to multi-site studies given “locality approval” by LRECs under the Annex D scheme prior to 1 March 2004. Such studies are likely to fall within the category now requiring site-specific assessment under SOPs (see paragraphs 4.19–4.32). However, the previous locality approval may not be quite in accordance with the new procedures. For example:

- There may not be a clearly defined Principal Investigator for the site
- The site may not be defined in accordance with the new guidance in section 4 of SOPs.

10.19 As a general rule, it should be assumed that the research has a valid ethical opinion for the site, however it has been defined. It is a matter for the sponsor to ensure that the local investigators comply with the protocol and other ethically approved documentation, and that they are accountable to the Chief Investigator whether directly or through an appointed Principal Investigator.

10.20 Where significant changes are proposed to the conduct of the research at the site, in particular the appointment of a new Principal Investigator, an application for SSA should be submitted by completing Part C of the new application form. The opportunity should be taken by the LREC to conduct a full SSA under SOPs and advise the main REC accordingly. This could include a re-definition of local research site(s) and designated Principal Investigators. These arrangements should then be confirmed in writing to the Chief Investigator by the main REC.

SSA exemption

10.21 An issue may arise in relation to SSA exemption where a main REC is appointed for a multi-site study with previous ethical approval from more than one LREC. The Chief Investigator may ask the main REC to consider designating the study as SSA-exempt, taking account of the guidance in paragraphs 4.19–4.32. If the main REC agrees, there would then be no requirement for the main REC to give an opinion on the extension of the study to other sites, and no need to apply for SSA.
Transfer of functions between RECs

10.22 The following guidance applies to all types of research.

10.23 The OREC Manager is responsible for arranging the transfer of functions from the “former REC” to the “new REC” in the following circumstances:

(i) Abolition of a REC by its appointing authority
(ii) Any other circumstance in which a REC ceases to operate (including mergers)
(iii) Revocation of recognition.

10.24 In the case of (i) and (ii) above, all studies for which the former REC was the main REC, and all outstanding applications, should be formally transferred to other appropriate RECs. In the case of (iii), only those CTIMPs that the REC is no longer recognised to review need to be transferred.

10.25 The choice of the new REC should take account of the following:

- In the case of CTIMPs, the new REC should be recognised for the appropriate type of research.
- Non-CTIMPs being conducted in more than one domain should normally be transferred to a MREC.
- As far as possible, studies should be transferred to new RECs within the same domain, or within the same OREC area.
- When transferring outside the OREC area, relevant OREC Managers should be consulted.

10.26 The new REC has full authority to give ethical opinions on outstanding applications, amendments or new sites.

10.27 In the case of outstanding applications, the new REC should continue to review the application in accordance with SOPs, taking account of the issues identified by the
former REC and information requested of the applicant. There is no provision for making a second request for information or extending the normal 60 day time period.
ANNEX A

INDEX TO STANDARD LETTERS AND FORMS

Validation of application

SL1 Acknowledgement of a valid application (study requiring SSA)
SL2 Acknowledgement of a valid application (SSA-exempt study)
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 No opinion pending consultation with referee
Annex Decision on SSA exemption

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
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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
SL21 Extension of favourable opinion to additional site(s) - re-issue of site approval form (SF1)
SL22 Extension of favourable opinion to additional site(s) - studies given ethical approval prior to 1 March 2004
SL23 Unfavourable opinion for site following objection from site-specific assessor

Projects outside the remit of NHS REC
SL24 Project not requiring review by a NHS REC
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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
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SL37  Acknowledgement of annual progress report
SL38  Reminder for annual progress report
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SL40  Acknowledgement of final research report
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Standard approval conditions

SL-AC1  Approval conditions (clinical trials of investigational medicinal products)
SL-AC2  Approval conditions (other research)

Forms for use by Co-ordinators

SF1  List of sites with a favourable ethical opinion
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 (COREC)
D.  Safety report form (COREC)

Forms for use by applicants (non-CTIMPs)

E.  Notice of substantial amendment (COREC)
F.  Declaration of the end of a study (COREC)
G.  Annual progress report form (COREC)
H.  Report of serious adverse event (COREC)
Forms A and B are Annexes 2 and 3 to ENTR/CT1 issued by the European Commission. The forms can be downloaded from the EudraCT website, see http://eudract.emea.eu.int/document.html#guidance.

All other forms are issued by COREC and can be downloaded from www.corec.org.uk.
ANNEX B

CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS IN HUMAN SUBJECTS

Standard conditions of approval by Research Ethics Committees

1. Further communications with the Research Ethics Committee

1.1 Further communications during the trial with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as “the Committee”) are generally the personal responsibility of the Chief Investigator. However, the submission of amendments (section 5), provision of pharmacovigilance reports (section 8) and notification of the conclusion or early termination of the trial (section 9) may be done either by the sponsor, the sponsor’s representative or Chief Investigator.

1.2 Where there is more than one sponsor for the trial, one of the co-sponsors should take responsibility for further communications with the Committee relating to each of the following group of functions:

- Substantial amendments, modified amendments and the conclusion of the trial
- Urgent safety measures
- Pharmacovigilance reporting.

2. Commencement of the trial

2.1 It is assumed that the trial will commence (i.e. the initiation of any protocol procedures) within 12 months of the date of the favourable ethical opinion.

2.2 It is assumed that the sponsor will obtain Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA) before the commencement of the trial. Evidence of the CTA should be forwarded when available (if not already provided to the Committee). Where the MHRA attaches conditions of approval that require substantial amendments to be made to the terms of the REC application or the supporting documentation, a notice of amendment should be submitted to the Committee (see section 5).

2.3 The study may not commence at any site until the Committee has notified the Chief Investigator that the favourable ethical opinion is extended to the site.

2.4 The study may not commence at any NHS site until the local Principal Investigator (PI) has obtained research governance approval from the relevant NHS care organisation.

2.5 Should the trial not commence within 12 months, the Chief Investigator should give the Committee a written explanation for the delay. It is open to the Committee to allow a further period of 12 months within which the trial must commence.
2.6  Should the project not commence within 24 months, the favourable opinion will be suspended and the application would need to be re-submitted for ethical review.

3.  Duration of ethical opinion

3.1  The favourable opinion for the research generally applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the Committee should be notified.

4.  Progress reports

4.1  Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. A progress report should be submitted to the Committee 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter until the end of the study is declared.

4.2  Progress reports should be in the format prescribed by COREC and published on the website (see www.corec.org.uk).

4.3  The Committee should be kept informed of any significant findings or recommendations by an independent Data Monitoring Committee or equivalent body established for the trial.

4.4  The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss the progress of the trial.

5.  Amendments

5.1  If the sponsor proposes to make a substantial amendment to the clinical trial authorisation, a notice of amendment should be submitted to the Committee and the MHRA. In the case of multi-site studies, there is no requirement to submit notices of amendment to LRECs undertaking site-specific assessment (SSA).

5.2  A substantial amendment is any amendment to the terms of the request for clinical trial authorisation, or to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the Committee, that is likely to affect to a significant degree:

(a)  the safety or physical or mental integrity of the trial participants
(b)  the scientific value of the trial
(c)  the conduct or management of the trial
(d)  the quality or safety of any investigational medicinal product used in the trial.

5.3  Notices of amendment should be in the format recommended by the European Commission at Annex 2 to “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) and available at http://eudract.emea.eu.int/document.html#guidance. The form should be signed by the person submitting the notice.

5.4 A substantial amendment on which an ethical opinion has been requested should not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the trial are urgent safety measures (see section 7). The Committee is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

5.5 Amendments that are not substantial amendments ("minor amendments") may be made at any time and do not need to be notified to the Committee.

6. Changes to sites

6.1 Where it is proposed to include a new site in the trial, Part C of the application form together with the Principal Investigator’s CV should be submitted to the relevant LREC for site-specific assessment (SSA). If the site was not included in the list of proposed trial sites in the original REC application and request for CTA, a notice of amendment should also be submitted to the Committee and the MHRA.

6.2 Where it is proposed to make important changes in the management of a site (in particular, the appointment of a new PI), a notice of amendment should be submitted to the Committee and the MHRA and a revised Part C for the site should be submitted to the relevant LREC for SSA, together with the CV for the new PI if applicable.

6.3 The Committee should be notified when a site is closed or withdrawn prematurely.

7. Urgent safety measures

7.1 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 trial participants against any immediate hazard to their health or safety.

7.2 The Committee and the MHRA must be notified within 3 days that such measures have been taken, the reasons why and the plan for further action.

8. Pharmacovigilance

8.1 Safety reporting requirements are set out in “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials of medicinal products for human use” (ENTR/CT3) issued by the European Commission and available at http://eudract.emea.eu.int/document.html#guidance. Guidance is also available on the COREC website.

8.2 Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the trial in the UK must be notified to the Committee and the MHRA in expedited fashion. A SUSAR which is fatal or life-threatening must be reported as soon as possible and in any event within 7 days after the sponsor became aware of the event. Any additional relevant information must be reported within 8 days of sending the first
report. A SUSAR which is *not* fatal or life-threatening must be reported as soon as possible and in any event within 15 days after the sponsor first became aware of the event.

8.3 There is no requirement to notify SUSARs occurring in the trial outside the UK or in other trials of the investigational medicinal product (IMP) in an expedited fashion.

8.4 There is no requirement to notify serious adverse events occurring in the trial, other than SUSARs.

8.5 For each IMP being tested in the trial, the sponsor must provide the Committee and the MHRA with an annual safety report of the safety of the subjects in clinical trials of the IMP for which it is the sponsor (whether in the UK or elsewhere). The report should include an aggregated global listing of all Suspected Serious Adverse Reactions (SSARs) occurring in those trials in the reporting period.

8.6 Where the sponsor is conducting one or more trials of the IMP outside the UK, it should also provide the Committee with quarterly safety reports, including a global line listing of all SUSARs occurring in relevant trials during the reporting period.

8.7 In the case of double-blinded trials, all reports of adverse reactions must be unblinded.

8.8 Pharmacovigilance reports may be provided to the Committee by either the sponsor, or the sponsor’s representative, or the Chief Investigator. All submissions should be accompanied by the cover sheet for safety reports published on the COREC website. A single cover sheet may be used for the submission of several reports.

8.9 The Chief Investigator and representatives of the sponsor may be requested to attend a meeting of the Committee or Sub-Committee to discuss any concerns about the health or safety of trial participants arising from pharmacovigilance reports.

8.10 Reports should not be sent to other RECs in the case of multi-site studies.

9. **Conclusion or early termination of the trial**

9.1 The sponsor should notify the Committee and the MHRA in writing that the trial has ended within 90 days of the conclusion of the research. Unless otherwise specified in the protocol, the conclusion of the trial is normally defined as the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. Any change to the definition of the conclusion of the trial should be notified to the Committee and the MHRA as a substantial amendment.

9.2 If the trial is terminated early, the sponsor should notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.3 Declarations of conclusion or early termination should be on the form issued by the European Commission at Annex 3 to ENTR/CT1 and available at http://eudraCT.emea.eu.int/document.html#guidance.
10. **Final report**

10.1 The sponsor or Chief Investigator should provide the Committee and the MHRA with a summary of the clinical trial report within 12 months of the conclusion of the trial. The Committee should also be notified of the arrangements for publication or dissemination of the research including any feedback to participants.

11. **Review of ethical opinion**

11.1 The Committee may review its opinion at any time in the light of any relevant information it receives.

11.2 The sponsor or Chief Investigator may at any time request that the Committee reviews its opinion, or seek advice from the Committee on any ethical issue relating to the trial.

12. **Protocol violation or breach of Good Clinical Practice**

12.1 The Committee should be promptly notified of any significant protocol violation or significant breach of Good Clinical Practice (GCP) that raises serious concerns about the suitability of a site or investigator, the safety of participants or the validity of the research data.

12.2 A minor deviation from the protocol to deal with unforeseen circumstances is not considered to be a protocol violation provided that it is approved by the Chief Investigator, either in advance or after the event. However, if the deviation would meet the criteria for a substantial amendment it should be notified to the main REC.

13. **Breach of approval conditions**

13.1 Failure to comply with these conditions may lead to suspension or termination of the favourable ethical opinion by the Committee and a recommendation to the Medicines and Healthcare products Regulatory Agency that the CTA should be suspended or terminated.
ANNEX C

RESEARCH IN HUMAN SUBJECTS OTHER THAN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

Standard conditions of approval by Research Ethics Committees

1. Further communications with the Research Ethics Committee

1.1 Further communications during the research with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as “the Committee”) are the personal responsibility of the Chief Investigator.

2. Commencement of the research

2.1 It is assumed that the research will commence within 12 months of the date of the favourable ethical opinion.

2.2 In the case of research requiring site-specific assessment (SSA) the research may not commence at any site until the Committee has notified the Chief Investigator that the favourable ethical opinion is extended to the site.

2.3 The research may not commence at any NHS site until the local Principal Investigator (PI) or research collaborator has obtained research governance approval from the relevant NHS care organisation.

2.4 Should the research not commence within 12 months, the Chief Investigator should give a written explanation for the delay. It is open to the Committee to allow a further period of 12 months within which the research must commence.

2.5 Should the research not commence within 24 months, the favourable opinion will be suspended and the application would need to be re-submitted for ethical review.

3. Duration of ethical approval

3.1 The favourable opinion for the research generally applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the Committee should be notified.

4. Progress reports

4.1 Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. The Chief Investigator should submit a progress report to the Committee 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter.
4.2 Progress reports should be in the format prescribed by COREC and published on the website (see www.corec.org.uk).

4.3 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss the progress of the research.

5. Amendments

5.1 If it is proposed to make a substantial amendment to the research, the Chief Investigator should submit a notice of amendment to the Committee.

5.2 A substantial amendment is any amendment to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the Committee, that is likely to affect to a significant degree:

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

(b) the scientific value of the trial

(c) the conduct or management of the trial.

5.3 Notices of amendment should be in the format prescribed by COREC and published on the website, and should be personally signed by the Chief Investigator.

5.4 A substantial amendment should not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the research are urgent safety measures (see section 7). The Committee is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

5.5 Amendments that are not substantial amendments (“minor amendments”) may be made at any time and do not need to be notified to the Committee.

6. Changes to sites (studies requiring site-specific assessment only)

6.1 Where it is proposed to include a new site in the research, there is no requirement to submit a notice of amendment form to the Committee. Part C of the application form together with the local Principal Investigator’s CV should be submitted to the relevant LREC for site-specific assessment (SSA).

6.2 Similarly, where it is proposed to make important changes in the management of a site (in particular, the appointment of a new PI), a notice of amendment form is not required. A revised Part C for the site (together with the CV for the new PI if applicable) should be submitted to the relevant LREC for SSA.

6.3 The relevant LREC will notify the Committee whether there is any objection to the new site or Principal Investigator. The Committee will notify the Chief Investigator of its opinion within 35 days of receipt of the valid application for SSA.

6.4 For studies designated by the Committee as exempt from SSA, there is no requirement to notify the Committee of the inclusion of new sites.
7. Urgent safety measures

7.1 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 research participants against any immediate hazard to their health or safety.

7.2 The Committee must be notified within three days that such measures have been taken, the reasons why and the plan for further action.

8. Serious Adverse Events

8.1 A Serious Adverse Event (SAE) is 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
   (f) is otherwise considered medically significant by the investigator.

8.2 A SAE occurring to a research participant should be reported to the Committee where in the opinion of the Chief Investigator the event was related to administration of any of the research procedures, and was an unexpected occurrence.

8.3 Reports of SAEs should be provided to the Committee within 15 days of the Chief Investigator becoming aware of the event, in the format prescribed by COREC and published on the website.

8.4 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss any concerns about the health or safety of research subjects.

8.5 Reports should not be sent to other RECs in the case of multi-site studies.

9. Conclusion or early termination of the research

9.1 The Chief Investigator should notify the Committee in writing that the research has ended within 90 days of its conclusion. The conclusion of the research is defined as the final date or event specified in the protocol, not the completion of data analysis or publication of the results.

9.2 If the research is terminated early, the Chief Investigator should notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.3 Reports of conclusion or early termination should be submitted in the form prescribed by COREC and published on the website.
10. **Final report**

10.1 A summary of the final report on the research should be provided to the Committee within 12 months of the conclusion of the study. This should include 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.

11. **Review of ethical opinion**

11.1 The Committee may review its opinion at any time in the light of any relevant information it receives.

11.2 The Chief Investigator may at any time request that the Committee reviews its opinion, or seek advice from the Committee on any ethical issue relating to the research.

12. **Breach of approval conditions**

12.1 Failure to comply with these conditions may lead to suspension or termination of the favourable ethical opinion by the Committee.
ANNEX D

Guidance from the European Commission on substantial amendments

Guidance from the European Commission on the notification of substantial amendments in clinical trials of investigational medicinal products is available in the following document:

“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)

Attachment 5 to the guidance lists examples of aspects of a CTIMP where amendments may need to be made, some of which may need to be notified as substantial. A copy of Attachment 5 is reproduced in this Annex. It should be consulted in conjunction with the guidance in paragraphs 5.29-5.35 of the SOPs on responsibilities for determining what is a substantial amendment.

The full text of ENTR/CT1 and other guidance issued on the European Directive is available on the EudraCT website:

http://eudract.emea.eu.int/document.html#guidance
ANNEX E

Notification of substantial amendments to CTIMPs

The sponsor of a clinical trial of an investigational medicinal product (CTIMP) is required to notify substantial amendments both to the MHRA and to 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.

In some cases, the amendment may be notified to either the MHRA or the main REC for information only.

It is the responsibility of the sponsor to decide whether a substantial amendment requires authorisation and/or an ethical opinion. However, sponsors may wish to take account of the following general guidance, which has been agreed between COREC and the MHRA.

(a) Amendments normally requiring authorisation only

- Amendments related to the quality of the IMP
- Changes to non-clinical pharmacology and toxicology data
- Changes to clinical trial and human experience data.

(b) Amendments normally requiring a favourable ethical opinion only

- Amendments to patient 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)
- Change of insurance or indemnity arrangements for the trial
- Change of the Chief Investigator or appointment of a key collaborator
- 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
• Any other amendments to the terms of the REC application.

(c) Amendments normally requiring both authorisation and a favourable ethical opinion

• Amendments related to the protocol (except those relating only to patient information sheets, consent forms, etc)
• Amendments related to the safety of the IMP
• Any other amendments related to the safety or physical or mental integrity of trial participants, or change to the risk/benefit assessment.
• Change of the sponsor or sponsor’s legal representative
• Change of the CRO assigned significant tasks
• Change of the definition of the end of the trial.

Where the amendment requires authorisation or ethical opinion only, the notice of amendment form must be sent to the other agency for information.

The issue of an updated Investigator’s Brochure for the IMP is not itself regarded as a substantial amendment unless there is a change to the risk/benefit assessment for the trial. There is no requirement to provide the MHRA or main REC with updated versions of the Investigator’s Brochure routinely or to seek authorisation or an ethical opinion.
ANNEX F

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 Annex G). 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/home/groups/l-unit1/documents/websiteresources/con009394.pdf

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. The algorithm is reproduced on the following page of this annex.
ANNEX G

Regulatory requirements for clinical investigations of medical devices

Legislation

1. 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.

2. The regulatory system in the UK is governed by the Medical Devices Regulations 2002. The Competent Authority for medical devices in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). MHRA (Devices) is a successor body to the previous Medical Devices Agency.

CE marking

3. Under the provisions of the Medical Devices Regulations, no medical device (with the exception of custom-made devices) may be placed on the EU market without a CE marking. For all except the very simplest devices, in order to obtain this marking, the manufacturer must go through a conformity assessment procedure to confirm that the device in question complies with the relevant essential requirements relating to safety and performance.

Clinical investigations involving non-CE marked devices

3. 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.

4. Under the provisions of the Medical Devices Regulations, the sponsor 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 MHRA (Devices).

5. MHRA (Devices) has 60 days in which to make an assessment of the information supplied as part of the notification and inform the applicant of any grounds for objection within that time period. 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.

6. As part of the final authorisation, MHRA (Devices) will require a copy of a favourable opinion from a relevant Research Ethics Committee. The ethical opinion can be obtained in parallel with the Competent Authority Notification.

7. The agreement of MHRA (Devices) is required for the extension of a clinical investigation to a new site, in addition to a favourable opinion from the main REC.

8. MHRA (Devices) must be notified of:

   • Any amendment to a clinical investigation, whether substantial or minor.

   • Any serious adverse event occurring in a clinical investigation, whether device related or not.

Clinical investigations involving CE marked devices

9. If a CE marked device is being used outside its intended purpose, or has been substantially modified, a Competent Authority Notification is required. The arrangements described in paragraphs 3-8 above apply.

10. For a clinical investigation involving a CE marked device being used for its intended purpose, the sponsor is not required to make a Competent Authority Notification.
Requirement for ethical review

11. Any clinical investigation of a device that meets the definition of research will need a favourable opinion from a NHS Research Ethics Committee in order to be conducted at NHS sites.
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