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Introduction to REC SOPs – version 3.4

Purpose and scope

1. The standard operating procedures (SOPs) in this document meet the obligations of the United Kingdom under Directive 2001/20/EC of the European Parliament and the Council of the European Union ("the EU Directive") for the operation of ethics committees in relation to clinical trials of investigational medicinal products (CTIMPs)[1].

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

3. The policy of the Department of Health, and of the devolved administrations (see paragraph 7), is that the operating procedures required by the EU Directive and the Clinical Trials Regulations should also apply in general to the review by RECs in the UK of all other research involving human participants within the NHS[2]; and to the review on a voluntary basis of research outside the NHS in the fields of health and social care[3] where the opinion of a NHS REC is sought by the researcher. There are some differences in operating procedures between CTIMPs and other research; these are indicated in the text where applicable.

4. The Department of Health has authorised the National Research Ethics Service (NRES) within the National Patient Safety Agency to co-ordinate the development of operational systems for NHS RECs, including systems to enable relevant committees to comply with the Clinical Trials Regulations. This role includes the development of a national set of standard operating procedures and the provision of operational advice and assistance.

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[1] In a separate Directive (Commission Directive 2005/28/EC), the European Commission has set out principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as requirements for authorisation of the manufacturing and importation of such IMPs.

[2] References in this document to the NHS should be taken to include the Northern Ireland Health and Personal Social Services.

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

5. These SOPs apply to all RECs that are established in accordance with GAfREC[1]. They apply both to:

- RECs that are recognised by the United Kingdom Ethics Committee Authority (UKECA) for the purpose of reviewing CTIMPs under the EU Directive from 1 May 2004 ("recognised RECs")[2]; and to
- RECs that are authorised by local appointing authorities or by the UK Health Departments under GAfREC to conduct the ethical review of health-related research either for a particular geographical area or for the entire United Kingdom ("authorised RECs").

6. Recognised RECs are required by the Clinical Trials Regulations to make standing orders and adopt standard operating procedures, subject to approval by UKECA, to enable them to meet their statutory obligations. The Department of Health has indicated that recognised RECs adopting the national SOPs can expect UKECA approval. Any recognised REC proposing to develop its own SOPs should notify the Operations Director of NRES so that arrangements can be made for these to be reviewed by UKECA.

7. The application of the SOPs to RECs in Scotland, Wales and Northern Ireland is by agreement of the following bodies:

- In Scotland, the Scottish Executive Health Department
- In Wales, the National Assembly for Wales Health Department
- In Northern Ireland, the Department of Health, Social Services and Public Safety.

8. These SOPs do not apply to:

- Clinical trials of medicinal products for gene therapy, which are covered by the Directive and the Clinical Trials Regulations but are subject to separate arrangements for ethical review. Applications relating to such trials should be submitted to the Gene Therapy Advisory Committee (GTAC), which is recognised

[1] *"Governance Arrangements for NHS Research Ethics Committees"* (GAfREC) was issued by the Department of Health in July 2001 and currently applies to all RECs in England. A revised version of GAfREC will be issued for consultation in 2005.
[2] Details of RECs currently recognised by UKECA are published on the NRES website.

as a specialist committee by UKECA under the Clinical Trials Regulations but is established by the Department of Health, and operates, under separate arrangements.

- Ethics committees established outside the NHS for the review of Phase 1 CTIMPs in healthy volunteers. A number of such committees are recognised by UKECA. Under the Clinical Trials Regulations, these committees must comply fully with the provisions of Schedule 2 for the establishment and operation of ethics committees, including approval of their standard operating procedures by UKECA.

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Implementation

9. Version 3.0 of the NRES SOPs came into effect on 25 July 2005. (The implementation date will be confirmed on the NRES website.) Where the SOPs state that a particular procedure "should" be followed - without qualification – all NHS RECs adopting the SOPs will be expected to comply fully. NRES Head Office will monitor compliance through the Offices of Research Ethics Committees (ORECs). The system of accreditation of NHS RECs being developed by NRES Head Office will be based on GAfREC and the SOPs.

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

11. The standard letters and forms listed in Annex A have been issued to REC Co-ordinators as a separate pack alongside these SOPs. The pack includes further guidance on use of the standard letter templates.

Standard approval conditions

12. The versions of the standard approval conditions (SL-AC1 and SL-AC2) attached at Annexes B and C superseded those issued in previous versions of the SOPs. They apply to all research being conducted with a favourable opinion from a NHS REC.

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Terminology

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

- Responsibilities assigned in the SOPs to the "Operations Director" at NRES may be delegated to another member of staff at NRES Head Office.
- All references in the SOPs to "the Chair" of the REC should be interpreted as referring also to the vice-Chair when acting in place of the Chair; or, if neither is available, to the alternate vice-Chair. If all three officers are unavailable, the REC's appointing authority may appoint another member of the Committee to perform the duties of the Chair until one of the other officers becomes available. When the Chair (or a vice-Chair) is in the chair, other officers resume their status as members.
- The "main REC" means the REC undertaking the ethical review of an application or, in the case of research that is underway, the REC that gave a favourable opinion. In the case of research studies with ethical approvals from more than one REC prior to 1 March 2004, one of the RECs should be appointed as main REC to review amendments (see paragraph 10.10).

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Superseded instructions and guidance

14. These standard operating procedures supersede the following paragraphs of the Governance Arrangements for NHS Research Ethics Committees (July 2001):

3.5-3.6, 6.10-6.11, 6.17, 7.5, 7.7, 7.9–7.15, 7.17–7.18, 7.23–7.35, 8.1–8.13, 9.1–9.6, 9.10, 9.19–9.23, 10.1–10.6.

15. In addition, the following guidelines and procedures no longer apply:

- All application forms used by RECs prior to the issue of the national electronic application form (version 3.0 dated January 2004)

- SOPs and standard letters previously adopted by RECs
- "Multi-centre Research Ethics Committees – Standing Orders" (DH, February 1998) insofar as they relate to the operating procedures of Type 3 RECs
- "Multi-centre Research Ethics Committees – Guidance for Researchers" (DH, October 2000)
- "Multi-centre research in the NHS – the process of ethical review when there is no local researcher" (Supplementary Operational Guidelines for NHS Research Ethics Committees, November 2000, version 2)
- The "Health Authority Locality Form" and associated procedures
- All other guidance on REC operating procedures published on the website of the Central Office for Research Ethics Committees (COREC) prior to 1 March 2004.

16. Version 3.4 of the SOPs incorporates Amendments 1-6 to version 3.0 of SOPs.

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Further information

17. RECs requiring further information or advice should in the first instance contact their OREC Manager.

18. Researchers and other enquirers may seek advice by contacting queries@nationalres.org.uk or the appropriate REC Co-ordinator.

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Terminology

Glossary

Adverse reaction	In a CTIMP, any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject. See also SSAR and SUSAR.
Amendment	A change made to the terms of the REC application, the protocol or any other supporting documentation after the study has started. A study is normally considered to start with the commencement of any protocol procedures.
Appointing Authority	A body responsible under GAfREC for the establishment and support of an NHS REC.
Appeal	Following the issue of an unfavourable opinion, the submission of the application without revision to another REC for a second ethical opinion.
Approval conditions	Conditions to be observed by the applicant in the conduct of the research. Approval conditions are issued by the REC 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.)*
ARSAC	Administration of Radioactive Substances Advisory Committee.
Authorised REC	A REC established under GAfREC but not recognised by UKECA . An authorised REC may review all applications except those relating to CTIMPs.
Booking	The booking of a new application or an appeal for review by a REC, and reservation of an agenda slot. Bookings may be

	made through CAS or direct to the office of a local REC, depending on the type of application.
Care organisation	The organisation(s) responsible for providing care to patients and/or users and carers participating in the study. Care organisations remain liable for the quality of care, and for their duty towards anyone who might be harmed by a study.
CAS	Central Allocation System, the booking system administered by NRES Head Office for applications to be reviewed by recognised RECs. Bookings of applications relating to a CTIMP or a multi-site study in two or more domains must be made through CAS. Multi-site studies in a single domain will normally be submitted direct to local RECs but may be allocated through CAS.
Chair	The member of a REC appointed to be Chair by the appointing authority. Where the Chair is unavailable for any reason, his/her duties may be performed by the vice-Chair or alternate vice-Chair.
Chief Investigator (CI)	The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.
CIOMS	Council for International Organisations of Medical Sciences.
Clinical Trials Regulations	The Medicines for Human Use (Clinical Trials) Regulations 2004.
Clock	The period allowed for the ethical review of a new application or substantial amendment. The clock starts on receipt of a valid application. See "60 day clock" and "35 day clock".
COREC	The Central Office for Research Ethics Committees (COREC) was the predecessor of NRES.

CTA	Clinical Trial Authorisation, the authorisation from the MHRA to conduct a CTIMP. No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the REC may be made in parallel.
CTIMP	Clinical trial of an investigational medicinal product. (Any other type of research is known as a non-CTIMP).
Domain	The area covered by a SHA (England), a Health Board (Scotland), a regional office of the NHS Wales Department or the whole of Northern Ireland.
Electronic signature	A digitally encrypted signature capable of verification by an independent service provider, in accordance with the Electronic Signatures Regulations 2002.
Employing organisation	An organisation employing the Chief Investigator, other investigators or research collaborators. Employers remain liable for the work of their employees.
EU Directive	Directive 2001/20 EC of the European Parliament and the Council of the European Union relating to the implementation of good clinical practice in the conduct of clinical trials of medicinal products for human use.
GAfREC	Governance Arrangements for NHS Research Ethics Committees.
IMP	Investigational medicinal product.
Investigator's brochure	A document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product which are relevant to the study of the product in human subjects.

Lead site	In the case of a multi-site study, the site for which the Chief Investigator is also the Principal Investigator.
Local collaborator	A person undertaking certain types of straightforward research procedure, not requiring the appointment of a Principal Investigator and a site-specific assessment (see "SSA-exemption"). Local collaborators at NHS sites should still seek approval from the R&D office.
Main REC	In the case of multi-site studies, the REC undertaking the ethical review of the application.
Medical Devices	See Annex G.
MHRA	Medicines and Healthcare products Regulatory Agency. MHRA (Medicines) is the competent authority for the UK in relation to the EU Directive and the Clinical Trials Regulations. MHRA (Devices) is the competent authority for the UK in relation to the Medical Devices Regulations 2002.
Minor amendment	An amendment which is not a substantial amendment, not requiring review by a REC (see paragraph 5.34).
Modified amendment	Following the issue of an unfavourable opinion on a substantial amendment, the re-submission of the amendment in modified form.
Non-CTIMP	Any research study that is not a CTIMP.
NPSA	National Patient Safety Agency.
NRES	National Research Ethics Service.
NRES Head Office	The part of NRES employed by NPSA, responsible for the operational management of NRES.

Operations Director	The senior manager at the NRES responsible for day-to-day operational management of the National Research Ethics Service.
OREC	Office for Research Ethics Committees, a network of offices under NRES Head Office responsible for professional oversight and support of all RECs in the UK. These structures will continue in shadow form until September 2007 and completion of transfer to the NRES structure.
Participant	Patient, service user, carer, relative of the deceased, professional carer, other employee, or member of the public, who consents to take part in a study. (Under the Clinical Trials Regulations, participants in CTIMPs are referred to as "subjects".)
Phase 1 trial	A clinical trial to study the pharmacology of an investigational medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial.
Principal Investigator (PI)	The investigator responsible for the research site where the study involves specified procedures requiring site-specific assessment (SSA). There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person.
Protocol	A document that describes the objectives, design, methodology, statistical considerations (or other methods of data analysis) and organisation of a research study.
Provisional opinion	A decision reached by a REC on an application, subject to the receipt of further information or clarification from the applicant. 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.
REC reference number	Reference number assigned by the REC accepting the application for review. This includes a REC local identifier, specific project number and year.
RED	The Research Ethics Database used by the REC system.
Receiving REC	The REC that first receives an application, whether or not it is then transferred to another REC for review.
Recognised REC	A REC legally recognised by UKECA to give an ethical opinion on a clinical trial of an investigational medicinal product (CTIMP) to be undertaken anywhere in the UK.
Referee	A person or body who gives expert advice to a REC on an application or any related matter.
Research site	The organisation or unit responsible for conducting any of the research procedures in a study at a particular locality.
Revision of application	Any changes made to the terms of an application at the request of the REC following the meeting or, following issue of an opinion, before the research has started. Revision is not permitted prior to the REC meeting once the application has been validated.
SAE	Serious Adverse Event (see statutory definition on page 26).
Second REC	The REC that reviews an application on appeal following the issue of an unfavourable opinion by the "first REC".
Single ethical opinion	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.

Site-specific assessor	The body responsible for undertaking a site-specific assessment, either an appropriate local REC or another body appointed by the OREC Manager.
60 day clock	The period of 60 calendar days allowed for the issue of an ethical opinion on a new application. The clock may stop once while awaiting a complete response from the applicant to one written request from the REC for further information or clarification.
SOPs	The Standard Operating Procedures issued by the NRES Head Office.
Sponsor	See statutory definition on page 26.
SSA	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 the Site-Specific Information 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 guidance in the NRES SOPs 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 local RECs at each site.
SSAR	Suspected Serious Adverse Reaction (see statutory definition on page 27).
SSI Form	Site-Specific Information Form
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 for the issue of an ethical opinion on a substantial amendment. The clock does not 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).

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Statutory definitions relating to CTIMPs

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

Authorised health professional

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

Note: The Chief Investigator and any investigator at a site in a CTIMP must be one of the above. See under "healthcare professional" for details of registration requirements.

Chief Investigator

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

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

Clinical trial

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

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products
(b) to identify any adverse reactions to one or more such products
(c) to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety or efficacy of those products.

Clinical trial protocol

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

Conducting a clinical trial

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

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

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

(d) Carrying out any test or analysis:

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

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

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

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

Healthcare professional

A healthcare professional means any of the following:

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

Other healthcare professionals	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, prosthetists and orthotists, radiographers, speech and language therapists.

Investigational medicinal product

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

(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation
(b) used for an indication not included in the summary of product characteristics under the authorisation for that product
(c) used to gain further information about the form of that product as authorised under the authorisation.

Investigator

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.

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