- Chapter 11, describing the criteria for approval of research.

12.50 The Secretary of State and the Welsh Ministers are required under section 32(3) of the Act to issue guidance on arrangements for nominating consultees where no willing personal consultee (e.g. a family member or other unpaid carer) can be identified. Draft guidance on nominated consultees has been published for consultation. Researchers will be required to have regard to the guidance once it is finalised.

12.51 The Medical Research Council is preparing detailed practical guidance for researchers on the research provisions of the MCA.

12.52 Summaries of the statutory criteria for section 30 and section 34 approval are available in the Tools area of the NRES website.

Adults with Incapacity (Scotland) Act 2000

12.53 The inclusion of participants unable to consent for themselves in research other than CTIMPs taking place in Scotland is governed by the Adults with Incapacity (Scotland) Act 2000 ("AWI Act").

12.54 Where any non-CTIMP is to be conducted at one or more sites in Scotland, the application should be booked through CAS. Under the AWI Act, the research must be approved by "the Ethics Committee" constituted by Scottish Ministers under Regulations made under the Act. This committee is currently the Scotland A REC. CAS should allocate all such applications to Scotland A REC, which will review the application under section 51 of the AWI Act.

12.55 The guidance relating to expert advice in paragraph 12.32 does not apply. The constitution of the Scotland A REC is determined by Regulations made under the AWI Act.

12.56 For procedures relating to research to be conducted in other UK countries as well as Scotland, see the guidance in paragraph 12.61.

(Back to Contents)

Northern Ireland

12.57 There is at present no specific legislation in Northern Ireland governing the inclusion in research of adults unable to consent for themselves. The legal position is determined solely by the common law.

12.58 Where any non-CTIMP is to be conducted at sites in Northern Ireland only, the application should be booked through CAS and allocated to one of the Health and Social Care (HSC) RECs.

12.59 The HSC REC should obtain expert advice before giving an opinion on the application. The guidance in paragraph 12.32 should be followed.

12.60 For procedures relating to research to be conducted in other UK countries as well as Northern Ireland, see the guidance in paragraph 12.61.

(Back to Contents)

Research other than CTIMPs: research conducted in different UK countries

12.61 The table below summarises application procedures for non-CTIMPs to be conducted in different UK countries. In particular, it gives guidance on applications conducted under more than one jurisdiction.

Countries where sites located	*Application process*
England and/or Wales only	Apply to any flagged REC in England or Wales.
Scotland only	Apply to Scotland A REC.
Northern Ireland only	Apply to any HSC REC in Northern Ireland.
England and Wales	Apply to any flagged REC in England or Wales.
England/Wales and Scotland	Two applications should be made: 1. The England/Wales application should be made to a flagged REC in England or Wales. 2. The Scotland application should be made to the Scotland A

	REC. Separate application forms should be submitted with separate REC reference numbers. The application form can be duplicated to minimise form-filling. The applications will be reviewed separately having regard to the relevant legislation. Any favourable opinion will apply only to England/Wales or Scotland respectively. Different opinions may be given.
England/Wales and Northern Ireland	Apply to any flagged REC in England or Wales. Only one application is required. The main REC will seek advice from a HSC REC on issues relating specifically to participants in Northern Ireland. Any advice will be incorporated in the main review.
Scotland and Northern Ireland	Apply to Scotland A REC. Only one application is required. The main REC will seek advice from a HSC REC on issues relating specifically to participants in Northern Ireland. Any advice will be incorporated in the main review.
England/Wales, Scotland and Northern Ireland	Two applications should be made: 1. Application for England/Wales/Northern Ireland should be made to a flagged REC in England or Wales. 2. Application for Scotland should be made to the Scotland A REC. Separate application forms should be submitted with separate REC reference numbers. The application form can be duplicated to minimise form-filling. The applications will be reviewed separately having regard to the relevant legislation. Any favourable opinion will apply only to England/Wales/Northern Ireland or Scotland respectively. Different opinions may be given.

(Back to Contents)

Site-specific assessment

12.62 SSA is required for any new application involving adults unable to consent for themselves (except for applications for section 30 approval under the MCA submitted under the transitional arrangements in paragraph 12.38).

(Back to Contents)

Addition of new sites

12.63 The usual SOPs apply to addition of new sites, except where the research is extended to a new country for the first time. The following situations should be noted:

- Where research is extended to England and Wales for the first time, a new application should be made to a flagged REC in England or Wales.

- Where research is extended to Scotland for the first time, a new application should be made to Scotland A REC.

- Where research is extended to Northern Ireland for the first time, an application for SSA should be made to a HSC REC. In addition to the usual documentation for SSA, information should be provided about the proposed recruitment procedures in Northern Ireland, together with a copy of the information sheet(s) and assent form(s) to be used. The SSA REC should conduct the SSA and, in particular, advise the main REC whether the recruitment procedures are suitable for Northern Ireland participants. If changes are required, objections may be raised with the main REC using SL20. The main REC should send SL23 to the CI including guidance on the changes required. The SSA may be re-submitted taking account of these changes.

(Back to Contents)

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

Correspondence with MHRA

SL16	Correspondence with MHRA

Site-specific assessment

SL17	Valid application for SSA
SL18	Invalid application for SSA
SL19	SSA – notification of no objection (for use where RED cannot be used to notify outcome of SSA electronically)
SL20	SSA – notification of objection
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
SL25	Ethical opinion by NHS REC on non-CTIMP outside the NHS

Withdrawal of application by researcher

SL26	Application withdrawn by researcher

Amendments

SL27	Acknowledgement of a valid notice of a substantial amendment
SL28	Invalid notice of a substantial amendment
SL29	Acknowledgement of substantial amendment to CTIMP notified for information only
SL30	Acknowledgement of minor amendment to a CTIMP
SL31	Acknowledgement of minor amendment to a non-CTIMP
SL32	Favourable opinion of a substantial amendment
SL33	Unfavourable opinion of a substantial amendment
SL34	Favourable opinion of a modified amendment
SL35	Unfavourable opinion of a modified amendment

Appeals

SL36	Confirmation of appeal by NRES Head Office
SL36A	Appeal disallowed
SL36B	Arrangements for appeal

Monitoring of approved research

SL37	Acknowledgement of annual progress report
SL38	Reminder for annual progress report
SL39	Acknowledgement of declaration of end of study
SL40	Acknowledgement of final research report
SL41	Reminder for final research report
SL42	Suspension or termination of favourable ethical opinion (non-CTIMP)
SL43	Notification of possible misconduct

Standard approval conditions

SL-AC1	Approval conditions (clinical trials of investigational medicinal products)
SL-AC2	Approval conditions (other specific research projects)
SL-AC3	Approval conditions (research tissue banks)

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 (NRES)
D.	Safety report form (NRES)

Forms for use by applicants (non-CTIMPs)

E. Notice of substantial amendment (NRES)
F. Declaration of the end of a study (NRES)
G. Annual progress report form (NRES)
H. Report of serious adverse event (NRES)

Forms A and 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 NRES and can be downloaded from www.nres.npsa.nhs.uk.

(Back to Contents)

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 responsibility of the lead sponsor. However, the sponsor may delegate responsibility to the Chief Investigator or another representative.

1.2 Where there is more than one sponsor for the trial, it is recommended that the lead sponsor or its representative takes responsibility for all communications with the Committee. However, one of the co-sponsors may take responsibility for 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 requests significant changes to the protocol before confirming CTA, or attaches any other condition requiring substantial amendments to be made to the terms of the REC

application or the supporting documentation, a Notice of Amendment form should be submitted to the Committee (see section 5).

2.3 The trial 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 trial may not commence at any NHS site until the local Principal Investigator (PI) has obtained approval from the R&D office for the relevant NHS care organisation.

2.5 Should the trial not commence within 12 months, the sponsor 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 trial not commence within 24 months, the Committee may review its opinion and may recommend to the MHRA that the CTA should be suspended or terminated.

3. Duration of ethical opinion

3.1 The favourable opinion generally applies for the duration of the trial. If it is proposed to extend the duration of the trial 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 trial. 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 trial is declared.

4.2 Progress reports should be in the format prescribed by NRES and published on the website at http://www.nres.npsa.nhs.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 form 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 RECs 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.

5.6 Further guidance on amendments is available at http://www.nres.npsa.nhs.uk.

6. Changes to sites

6.1 Where it is proposed to include a new site in the trial, the Site-Specific Information Form (SSI Form) together with the Principal Investigator's CV should be submitted to the relevant REC 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 form should also be submitted to the Committee. A copy of the Notice of Amendment should be sent to the MHRA for information only.

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 form should be submitted to the Committee (and to the MHRA for information) *and* a revised SSI Form for the site should be submitted to the relevant REC 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://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf. Guidance is also available on the NRES 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 a commercial sponsor is conducting one or more trials of the IMP outside the UK, it should also provide the Committee with 6 monthly 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 NRES 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 trials.

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. It has no power to legally withdraw the opinion it has given but may draw the attention of the MHRA to any serious concerns and may recommend that consideration is given to suspending or terminating the CTA.

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. Serious breaches of Good Clinical Practice or the protocol

12.1 The Committee should be promptly notified of any serious breach of the conditions or principles of Good Clinical Practice (GCP) or of the protocol. A breach should be regarded as serious if it is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. The sponsor should notify the Committee and the MHRA in writing within 7 days of the matter coming to their attention. There is no requirement to notify minor breaches of GCP or the protocol.

12.2 A minor deviation from the protocol to deal with unforeseen circumstances is not considered to be a serious breach of the protocol 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 Committee.

12.3 There is no statutory provision for the Committee to approve proposed deviations from the protocol for individual subjects. It is the responsibility of the sponsor to consider whether protocol amendments should be made in such cases. Where the amendment is substantial, it should be notified.

13. Breach of approval conditions

13.1 These approval conditions are not legally binding but they set out important guidance which Chief Investigators and sponsors are expected to follow. Failure to comply with the conditions may lead to a change of the Committee's opinion and a recommendation to the MHRA that the CTA should be suspended or terminated.

(Back to Contents)

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 NRES and published on the website (see www.nres.npsa.nhs.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 NRES 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. The SSI Form together with the local Principal Investigator's CV should be submitted to the relevant local REC 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 SSI form for the site (together with the CV for the new PI if applicable) should be submitted to the relevant local REC for SSA.

6.3 The relevant local REC 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 NRES 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.