9.3 Reports of conclusion or early termination should be submitted in the form prescribed by NRES 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.

(Back to Contents)

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

(Back to Contents)

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 NRES 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.

(Back to Contents)

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://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrialdir_auth.htm#1

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.

(Back to Contents)

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

4. 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.

5. 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).

6. 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.

7. 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.

8. 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.

9. 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

10. 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.

11. 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

12. 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.

(Back to Contents)

ANNEX H

Statutory requirements relating to research involving human tissue

1. The Human Tissue Act 2004

1.1 The Human Tissue Act 2004 ("the HT Act") is a framework for regulating the storage and use of human tissue from the living, and the removal, storage and use of tissue and organs from the deceased, for specified health-related purposes and public display.

1.2 The HT Act makes consent the fundamental principle underpinning the lawful retention and use of body parts, tissue and organs from the living or the deceased for specified purposes (known in the Act as "scheduled purposes"). Consent is also required for the removal of such material from the deceased. It does not cover removal of such material from the living – consent for this continues to be required under common law.

1.3 One of the scheduled purposes under the HT Act is "research in connection with disorders or the functioning of the human body". References to "research" in this Annex and in section 11 of the SOPs mean research included within this definition.

1.4 The HT Act establishes the Human Tissue Authority (HTA) to advise on and oversee compliance with the HT Act. The Authority issues good practice guidance in the form of Codes of Practice, which are laid before Parliament. The first series of codes of practice have been published at www.hta.gov.uk. The most important of these for the purpose of ethical review is the Code of Practice on Consent. The HTA will also license and inspect a range of activities including the storage of human tissue for research.

1.5 Most parts of the HT Act were brought into force on 1 September 2006 by Regulations made under the Act. *With the exception of the provisions on genetic/DNA analysis (see paragraphs 1.16-1.18) and storage of relevant material for transplantation , the Act extends to England, Wales and Northern Ireland only*.

Definition of relevant material

1.6 Human tissue and cells are referred to in the HT Act as "relevant material". This is generally defined in the Act as any material that has come from a human body and consists of, or includes, human cells. The HTA defines cells as "individual human cells or a collection of human cells when not bound by any form of connective tissue". This definition excludes cell lines. Other exceptions to the definition in the Act (except in relation to DNA analysis) are hair and nail of living people, embryos outside the body and gametes. Embryos created outside the body, and gametes, are covered by separate legislation.

1.7 More detailed guidance on what is, or is not, relevant material will be published on the HTA website (www.hta.gov.uk) and in the Data and Tissues Toolkit being developed for publication by the Medical Research Council.

1.8 The statutory definition of relevant material should be applied in the same way to the definition of the tissue of NHS patients for the purpose of determining whether ethical review is required under NHS research governance systems and GAfREC.

Consent to use of tissue in research

Legal requirements

1.9 Under the HT Act there is a general requirement to obtain "appropriate consent" (see paragraph 1.12 below) in order to store or use human tissue for scheduled purposes. The HT Act provides a number of exceptions to this rule. In relation to research, the most important exceptions are:

(i) Existing holdings

Under section 9 of the HT Act it is lawful to retain and use, without consent, human tissue already held in storage for research purposes on the day before the Act came into effect ("existing holdings"). This applies to tissue from the living or the deceased. It does not however imply that such tissue can be freely used without regard to ethical consideration (see paragraph 11.10 of the SOPs).

(ii) Tissue from the living

Under section 1(9) of the HT Act it is lawful to store and use for research, without specific consent for this purpose, tissue which has been lawfully removed from the living for other purposes, e.g. any surplus (or "residual") tissue taken with consent for diagnostic or therapeutic purposes in the course of normal clinical care and which is left over from these procedures. The conditions are that the research must be ethically approved by a REC or other research ethics authority and the researcher must not be able to identify the tissue donor or be likely to be able to do so in future.

(iii) Imported material

It is lawful to store and use for research, without consent, human tissue which has been imported but the importer should comply with the best practice set out in the HTA Code of Practice on the import and export of human bodies, body parts and tissue. (The draft Code of Practice was published for consultation on 3 October 2006.)

(iv) 100 year rule

It is lawful to store and use for research, without consent, human tissue from the body of a person who died before 1 September 2006 and at least 100 years have elapsed since their death.

1.10 *Consent continues to be required under the common law to remove any bodily material from living persons*. In some cases, consent may explicitly be sought to remove the tissue for research purposes. Alternatively, consent may be sought to remove the tissue for diagnostic or therapeutic purposes; the surplus tissue may then be used lawfully in research without specific consent subject to the conditions in section 1(9) of the HT Act (see 1.9(ii) above).

1.11 Table 1 summarises legal requirements under the HT Act and the common law for consent to remove, store or use tissue, or analyse DNA in bodily material, for research purposes. (In relation to DNA analysis, bodily material includes the hair and nail of living persons and gametes.) *It should be noted that, even where there is no legal requirement for consent, there will still be a requirement to hold a licence from*

the HTA to store the tissue for use in research or to seek/obtain ethical approval to qualify for exemption from licensing (see paragraphs 1.25-1.27).

Table 1: Summary of legal requirements for consent to remove, store or use tissue or analyse DNA in bodily material for research purposes

Scenario	*Consent legally required?*
Storage or use of existing holdings	No
Analysis of DNA in existing holdings	No
Storage or use of imported tissue	No (but good practice for importer to seek evidence of consent – see draft HTA Code of Practice)
Storage or use of tissue from a deceased person who died more than 100 years ago	No
Storage or use of tissue from the living (not identifiable to the researcher)	No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)
Analysis of DNA in tissue from the living (not identifiable to the researcher)	No, provided the research is ethically approved (either by project-specific approval or via generic approval for a RTB providing the tissue)
Storage or use of tissue obtained from a deceased person who died less than 100 years ago	Yes
Storage or use of tissue from the living (identifiable to the researcher)	Yes
Removal of tissue from the living	Yes (under common law)
Removal of tissue from the deceased	Yes
Analysis of DNA in tissue from the living (identifiable to the researcher)	Yes
Analysis of DNA in tissue obtained from a deceased person who died less than 100 years ago or after 1 September 2006	Yes

1.12 On consent practice, the HTA encourages informed and generic consent to use of tissue in research to be sought at the outset from donors as the default position. This allows tissue to be used for different research projects over an unspecified period of time and mitigates the need to obtain repeat consent for each and every research project. Further guidance is available in the HTA Code of Practice on Consent.

Appropriate consent

1.13 The HT Act identifies the person who can give "appropriate consent" where this is required for lawful storage or use of tissue for research. Table 2 summarises who can give appropriate consent under the Act.

Table 2: Appropriate consent

The person	*Who gives consent*
Living adult, or living child[1] with capacity and willing to make a decision	His/her own consent
Living child[1] who lacks capacity to give consent or who has capacity but is unwilling to make a decision	A person with parental responsibility
Deceased adult	(i) His/her own consent before death. (ii) If no prior consent by the deceased adult, the consent of a nominated representative. (iii) If no representative was appointed by the deceased person, a person in a qualifying relationship.
Deceased child[1]	(i) A person who had parental responsibility immediately before the child's death. (ii) If no person had parental responsibility, another person in a

[1] The HT Act defines a child as a person under the age of 18.

	qualifying relationship.
Living adult who lacks capacity to give consent	See paragraph 1.15 below.

1.14 Persons in a *qualifying relationship* are ranked in the following order where consent is sought to store or use human tissue from the deceased:

(a) Spouse or partner (including civil partners)
(b) Parent or child
(c) Brother or sister
(d) Grandparent or grandchild
(e) Child of a brother or sister
(f) Stepfather or stepmother
(g) Half brother or half sister
(h) Friend of long standing.

1.15 Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.

Adults with incapacity in England, Wales and Northern Ireland

1.16 Where consent is required to store or use tissue from the living in research but the person is an adult (aged 16 or over) without the capacity to give consent, the position in England and Wales will be governed by the Mental Capacity Act 2005 (MCA) once it comes into effect (scheduled for 1 April 2007). Ethical approval from a REC will be required under section 30 of the MCA. (Further SOPs will be issued about the implementation of the MCA.) In the interim, before section 30 of the MCA comes into force, a person without capacity will be deemed to have consented to the storage and use of their tissue if it is in connection with one of the following:

(a) A CTIMP which is authorised and conducted in accordance with the Clinical Trials Regulations (which requires consent from a "legal representative"), or
(b) Any other research which is ethically approved by a REC and meets the following criteria:
    (i) the research is in connection with the disorders, or the functioning of, the human body

(ii) research of comparable effectiveness could not be carried out if confined to persons with capacity to consent

(iii) research of comparable effectiveness could not be carried out using tissue anonymised to the researcher.

1.17 The Mental Capacity Act does not apply in Northern Ireland. The law on mental capacity in Northern Ireland is to be reviewed but the present position is governed entirely by the HT Act. In Northern Ireland a person without capacity will be deemed to have consented to the storage and use of their tissue in research where either of the conditions in 1.16 apply. This will remain the case after the MCA comes into force.

1.18 Research using the tissue of adults without capacity in Scotland will continue to be governed by the Adults with Incapacity (Scotland) Act 2000.

Consent to analysis of DNA (applies also in Scotland)

1.19 The HT Act makes it an offence to have human tissue (which in this particular context includes the hair and nail of living persons and gametes) with the intention of analysing its DNA or using the results of the analysis without consent unless for an excepted purpose. *This provision applies UK-wide*. However, the effect of the exceptions is that it is not an offence to analyse DNA without consent in research if any of the following apply:

- The tissue is an existing holding (i.e. held before 1 September 2006) and the results of the analysis are to be used for the purposes of research.
- The tissue is obtained on or after 1 September 2006 from the body of a living person and the researcher is not likely to come into possession of the identity of the donor and the research is ethically approved.
- The tissue is an embryo outside the human body.
- The tissue is from the body of a person who died before 1 September 2006 and at least 100 years have elapsed since their death.

1.20 Therefore consent *is* required to analyse DNA or use the results of the analysis for research purposes in each of the following cases:

- The tissue is obtained on or after 1 September 2006 from a living person in the UK and the researcher knows, or is likely to know, the identity of the donor.
- The tissue is obtained on or after 1 September 2006 from a living person in the UK and the research is not ethically approved.
- The tissue is obtained on or after 1 September 2006 from a deceased person who died before 1 September 2006 and less than 100 years have elapsed since their death.
- The tissue is obtained from a deceased person who died on or after 1 September 2006.

1.21 Where consent is required, the requirements for "qualifying consent" are similar to those for "appropriate consent" in the case of tissue (see paragraphs 1.13-1.14). However, for the purpose of consent to analyse the DNA in the tissue of a deceased person, the consent of any person in a qualifying relationship is enough – the list of relatives is unranked in this case. In the case of adults without capacity to give consent, there are distinct provisions in relation to England and Wales; Northern Ireland; and Scotland.

Further guidance on consent

1.22 The HTA Code of Practice on Consent gives detailed guidance on issues of consent under the HT Act. It explains the legal requirements in detail but goes further in establishing standards for obtaining consent and promoting good practice. The Codes of Practice are not legally binding but their advice represents best practice and should be considered carefully by all those concerned, including tissue bank managers, researchers and ethics committees. The HTA may take account of adherence to the Codes of Practice when it makes licensing decisions.

1.23 A summary of the consent provisions of the Act will be available in the Data and Tissues Toolkit being developed by the Medical Research Council.

Licensing

1.24 The HTA has powers under the HT Act to license a range of activities involving human tissue, and to conduct inspections to ensure compliance with the Act, codes of practice and licensing conditions.

1.25 The activities for which a licence is required include:

- Removal of tissue from the body of a deceased person for research purposes (unless the person died before 1 September 1906)
- Storage of tissue for use for research purposes (except as specified in paragraph 1.26).

1.26 Where tissue is taken in the course of normal clinical care and is stored as part of a clinical diagnostic archive, storage of that tissue is not licensable. The primary purpose for holding the tissue is the diagnostic archive. If slivers of tissue taken from blocks stored as part of the diagnostic archive are then used for research, no licence would be needed; the primary purpose for holding tissue would still be diagnostic. However, where tissue is removed for diagnosis but extra material is taken to store for use in unspecified research, storage of that material would be licensable. In this case the primary purpose would be both diagnostic and research.

1.27 Under the Regulations made under the HT Act, storage of tissue is exempt from the licensing requirements where it is:

- For the purpose of research which is ethically approved (including where ethical approval was given before the commencement of the HT Act)
- For the purpose of a specific research project for which ethical approval is pending (i.e. an application for ethical approval has been submitted but a final opinion has not yet been given).

1.28 The effect of these provisions is that research tissue banks (storing tissue for unspecified research projects) will be licensed but storage of tissue by end user researchers for ethically approved projects will not be licensable.

1.29 The HTA will issue licences to store tissues or cells for research purposes following a process of self-assessment by the establishment (in the form of a Compliance Report) and review by the Authority. The authority conferred by a licence is given to the "Designated Individual" (the person under whose supervision the licensed activity is to be undertaken), any other designated person, and any person acting under the direction of the Designated Individual or a designated person. The Designated

Individual has a statutory duty to ensure the suitability of the persons and premises covered by the licence and that all conditions are complied with. More information is available in the HTA's guide to licensing for Designated Individuals and Licence Holders.

1.30 Compliance reports will provide information to the HTA on how the establishment meets the requirements of the HT Act and standards of good practice in the following areas:

- Consent
- Governance and quality systems
- Premises, facilities and equipment
- Disposal.

1.31 Further detailed guidance about licensing requirements is available on the HTA website (www.hta.gov.uk). A summary will be available in the Data and Tissues Toolkit.

2. Human Tissue (Scotland) Act 2006

2.1 The Human Tissue (Scotland) Act 2006 (referred to in this section as "the Act") includes certain provisions relating to research using tissue and organs from the deceased. Unlike the Human Tissue Act 2004 it does not deal at all with research using tissue from the living. The Scottish Executive intends issuing guidance on research using tissue from the living in the near future.

2.2 Detailed guidance on the Act has been issued by the Scottish Executive in HDL(2006)46, which is available on the Scottish NHS website at: http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf

The following paragraphs provide an overview of the provisions relating to research.

Authorisation to use human tissue for research

2.3 Under Section 3 of the Act, part of the body of a deceased person may be removed from the body and used for certain purposes (including research) where the removal

and use for this purpose is "authorised". Sections 6-10 of the Act make detailed provisions for such authorisation:

- Section 6 provides for authorisation by an adult of the removal and use of part of the adult's own body after death.
- Section 7 provides for authorisation by the nearest relative of a deceased adult.
- Section 8 provides for authorisation by a child aged 12 or over of the removal and use of part of the child's body after death.
- Section 9 provides for authorisation by a person with parental rights and responsibilities in respect of a child who has died aged 12 or over.
- Section 10 provides for authorisation by a person with parental rights and responsibilities in respect of a child who has died under the age of 12.

2.4 The above provisions do not apply in relation to tissue samples and organs removed during post-mortem examinations. Nor do they apply to the body of a deceased person who died before 1 September 2006 and at least 100 years have elapsed since their death.

2.5 Under Section 38, a tissue sample removed from the body of a deceased person (or from an organ removed from the body) during a post-mortem examination and no longer required by the Procurator Fiscal becomes part of the medical records of the deceased persons. Section 39 allows such samples to be used for certain purposes (including research) where use for this purpose is authorised. Sections 42-46 contain provisions for authorisation similar to those in Sections 6-10.

2.6 Under Section 40 of the Act, an organ removed from the body of a deceased person during a post-mortem examination and no longer required by the Procurator Fiscal may be retained and used for certain purposes (including research) provided that:

- The subsequent use of the organ for this purpose is authorised in accordance with Sections 42-46, and
- The research is approved in writing by such persons or groups as the Scottish Ministers may specify (see paragraph 2.6 below).

2.7 Under Scottish law a child is defined as a person aged under 16.