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

(a) The Site Specific Information Form has been submitted.

(b) All relevant sections and questions in the SSI form have been completed, and the text is in English and legible.

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

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

(e) 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.

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

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

4.42 If the application is valid, the SSA REC 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.

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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 SSA REC 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 SSA REC. However, if the main REC does not accept the reasons given in A29 and requires their inclusion, the SSI 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 the SSI form to the R&D Office 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.

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Procedures for site-specific assessment by a REC

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

4.49 Where a REC 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 REC.

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 REC. 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 the SSI form of the application form is a member or deputy member of the SSA REC, the SSA should normally remain the responsibility of the REC to which it is submitted. The member or deputy member concerned should take no part in the assessment other than providing additional information at the request of the assessors. He/she may attend any meeting to answer questions but should leave the meeting room while the assessment is discussed and a decision made.

4.52 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 SSA REC 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 SSA REC 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 SSA REC has no objections to the research on site-specific grounds, the 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 Co-ordinator may send SL19 by letter or e-mail.

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

4.56 The SSA REC (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 SSA REC has any concerns about the research that are not directly relevant to the SSA, it may separately refer these to the main REC in writing. The SSA REC should not, however, delay the SSA or raise formal objection to the research being conducted at the site on the basis of these concerns. It is entirely a

matter for the main REC to consider any matters that are raised in this way as part of the process of ethical review.

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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 Office 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 REC in the area, or of both REC 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 SSA REC 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 SSA REC Co-ordinator in writing within 25 days of the receipt of the valid application.
- The SSA REC Co-ordinator to retain responsibility for notifying the outcome of the SSA to the main REC and for use of RED.
- There may be further discussion of the SSA directly between the main REC and the assessors, in particular where the main REC is considering over-ruling objections, but the SSA REC and the 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.

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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 SSA REC. 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.

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

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

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

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

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 SSA RECs to explain the concerns that have arisen. SSA RECs 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.

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

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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 SSA REC in the SSI form may no longer be complete or accurate. In such cases, the main REC should consider the following options:

- Where the revisions are ethically acceptable but in the judgement of the main REC the implications for site-specific assessment are minor (e.g. modification of the schedule of study procedures), any SSAs already underway should continue based on the existing version of the SSI form. However, the Chief Investigator may be required to send an amended version of the SSI form *for information only* to SSA REC that have already received applications for SSA, with a covering letter highlighting the changes. (Any SSA REC 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 SSI form.

- Where the revisions are ethically acceptable but could have significant implications for the site-specific assessment, the Chief Investigator may be required to revise the SSI form 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 SSI Forrms should be given a new SSA reference by SSA RECs. This option, which will delay the process of approving sites, should only be taken exceptionally where the existing version of the SSI form 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 the SSI Form.

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Unfavourable opinion on the main application

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

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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.

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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.

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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.

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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 SSA REC is responsible for proactive monitoring of the conduct of the research at individual sites. However, where information comes to the attention of either REC that raises questions about the suitability of the site or investigator, the favourable opinion for the site may be reviewed.

4.82 Where concerns are drawn to the attention of the SSA REC, it may review the original site-specific assessment or request further advice from a delegated assessor. The

SSA REC or delegated assessor may seek further information from the Principal Investigator and/or request submission of a new SSI Form or CV if necessary. If it is not possible to resolve the concerns, the SSA REC should bring them to the attention of the main REC as soon as possible. The 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 SSA REC.

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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.

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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 SSA REC in Scotland and processed in the normal way.

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Research governance approval by care organisations

4.86 Research governance approval should be sought from the R&D Office 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 Office. 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 Offices of care organisations about proposed research or instigating research governance approval procedures (see paragraphs 3.61-3.62).

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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).

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Providing SSA to ethics committees outside the NHS

4.90 SSA RECs 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 medicinal products for gene therapy being reviewed by the Gene Therapy Advisory Committee (GTAC).

4.91 The SSA REC 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 NRES. 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.

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Section 5: Amendments to research given a favourable opinion

Summary

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 NRES 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 local RECs.

Guidance is given on proposed amendments that may warrant a new application.

Urgent safety measures may be taken to protect participants from an immediate hazard to their welfare or safety. The main REC must be notified within 3 days.

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).

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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.

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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.

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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 NRES Notice of Amendment form should be used. This is published on the NRES 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 local RECs 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.

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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 NRES and the MHRA.

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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