the quality of the IMP), the Co-ordinator should acknowledge receipt within 30 days by sending SL29 to the sponsor (or other person submitting the notice on behalf of the sponsor).

5.21 The amendment should be seen and noted by the Chair. There is normally no requirement to notify the Committee. However, if the Chair considers exceptionally that the amendment could affect the ethical opinion as well as the clinical trial authorisation, the matter may be discussed at a meeting of the sub-committee or Committee. A letter may be sent to the sponsor advising that, in the view of the REC, an ethical opinion should have been requested and making any comment on ethical issues raised by the amendment. A REC may review its opinion of a study at any time and may suspend or terminate a favourable opinion if serious concerns arise (paragraphs 9.78-9.84). Although in the case of a CTIMP it is primarily for the sponsor to interpret the guidance on the need for ethical review of amendments, the REC may review any information it receives.

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

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Validation of notice of amendments

5.23 The period of 35 days, within which an ethical opinion must be given, normally begins when a valid notice of amendment is received by the main REC. (However, special procedures apply where the amendment requires an application for SSA – see paragraph 5.62.)

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

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

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

(b) Relevant extracts or new versions of modified documents have been submitted, showing the new version number and date and giving both the previous and new wording.

(c) The notice of amendment has been signed by the appropriate person.

5.26 It is the responsibility of the Co-ordinator of the main REC to decide whether or not the notice of amendment is valid and to notify the sponsor and Chief Investigator using SL27 (valid notice) or SL28 (invalid notice). Notification should normally be given within 5 working days of receipt. (However, it is not necessary for the main REC to validate notices of amendment where an application for SSA is required – see paragraph 5.62.)

5.27 Where the notice is sent to another REC in error, the Co-ordinator should notify the Chief Investigator as soon as possible that it should be re-submitted to the main REC. The Co-ordinator may offer to send on the documentation. The validation date will be the working day on which the main REC receives the documentation.

5.28 The decision whether or not a notice of amendment is valid should normally be made by the REC Co-ordinator. The agreement of the Chair is not required. The Co-ordinator may however seek the advice of the Chair if, in the case of an amendment to a study other than a CTIMP, it appears that the amendment is not substantial and does not require ethical review (see paragraphs 5.31-5.34).

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Deciding whether an amendment is substantial

Clinical trials of investigational medicinal products

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

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

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Other research

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

5.32 In making this judgement, consideration needs to be given to whether the proposed changes will affect the research "to a significant degree". Particular account should be taken of any implications for the safety or welfare of participants, and of any information that participants might require to give informed consent to continue to participate in the research as amended. It is recommended that where there is any doubt about the potential implications of the amendment for participants, it should be treated as a substantial amendment and ethically reviewed by the REC.

5.33 The following changes should normally be regarded as substantial:

- Changes to the design or methodology of the study, or to background information affecting its scientific value
- Changes to the procedures undertaken by participants
- Any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study
- Changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers
- A change of sponsor(s) or sponsor's legal representative
- Appointment of a new Chief Investigator or key collaborator, or temporary arrangements to cover the absence of a CI
- A change to the insurance or indemnity arrangements for the study
- Inclusion of a new research site (not listed in the original application) in a study requiring SSA (see paragraph 5.62)
- Appointment of a new Principal Investigator at a research site (see paragraph 5.69)
- A significant change to the definition of a research site requiring SSA (see paragraph 5.71)
- A change to the "SSA-exempt" status of a study (see paragraph 4.23)
- A change to the definition of the end of the study (see paragraph 9.73)
- Any other significant change to the protocol or the terms of the REC application.

5.34 There will, however, be changes to the details of research that have no significant implications for participants or for the conduct, management or scientific value of the study and can be regarded as non-substantial or minor amendments. Examples might be as follows:

- Correction of typographical errors in the protocol or other study documentation
- Other minor clarifications of the protocol
- Changes to the Chief Investigator's research team (other than appointment of key collaborators)
- Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator)

- Changes in funding arrangements
- Changes in the documentation used by the research team for recording study data
- Changes in the logistical arrangements for storing or transporting samples
- Inclusion of new sites in SSA-exempt studies (see paragraph 4.20)
- Extension of the study beyond the period specified in the application form (see paragraph 9.10)
- Issue of an updated Investigator's Brochure or Summary of Product Characteristics relating to an investigational medicinal product.

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

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Notification of minor amendments

5.36 Where changes are made to a research study that the sponsor (or Chief Investigator) considers minor rather than substantial amendments, there is no requirement to obtain an ethical opinion. They may be notified to the main REC for information, and this may be helpful where the change relates to the contact details for the study or involves updating the information sheet or consent form for participants. Where minor amendments are notified, the sponsor or Chief Investigator should do so by letter rather than by submitting a notice of amendment form. It is helpful if the letter states clearly that the amendment is not considered to be substantial and an ethical opinion is not required.

5.37 Minor amendments should be noted by the Chairman but do not need to be reported to the Committee. The Co-ordinator should acknowledge receipt of any minor amendment within 35 days using SL30 (CTIMPs) or SL31 (non-CTIMPs).

5.38 Where a sponsor or Chief Investigator notifies the main REC of a minor amendment, but the Chair considers that it should have been regarded as substantial and requires

ethical review, the matter may be discussed at a meeting of the sub-committee or Committee. A REC may review its opinion of a study at any time and may suspend or terminate a favourable opinion if serious concerns arise (paragraph 9.78-9.84). Although in the case of a CTIMP it is primarily for the sponsor to interpret the guidance on what is substantial, the REC may review any information it receives.

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

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Requests for advice on whether an amendment is substantial

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

- In the case of a CTIMP, it should be advised that this is a matter for the sponsor, although the guidance for RECs in paragraphs 5.33-5.34 may be voluntarily taken into account.
- In the case of any other research, the Co-ordinator may give advice on behalf of the REC, or refer the matter to the Chair. If in any doubt about the matter, the Chief Investigator should be required to submit a notice of amendment for review.

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Review of substantial amendments

5.41 Except where paragraphs 5.45 or 5.48 apply, substantial amendments should be reviewed by a sub-committee of the relevant REC (see Section 6) or exceptionally by the Committee itself. They may not be reviewed by the Chair acting alone, except where the Chair has been given delegated authority at a meeting to review a modified amendment (see paragraph 5.48).

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

5.43 The decision reached at the meeting should normally be either a favourable or unfavourable opinion of the amendment. The Co-ordinator should notify the sponsor and Chief Investigator of the decision using one of the following letters:

SL32 Favourable opinion of substantial amendment
SL33 Unfavourable opinion of substantial amendment

5.44 In the case of CTIMPs, the main REC is required by the Clinical Trials Regulations to notify the MHRA of its opinion on the substantial amendment, whether favourable or unfavourable, so that it can be entered on EudraCT. A copy of the opinion letter should be sent by email to clintrialhelpline@mhra.gsi.gov.uk with the subject line "REC opinion for EudraCT" (see footnote to paragraph 3.63E). Where the MHRA has been asked to authorise a substantial amendment, it will issue a written notice within 35 days accepting the amendment or giving grounds for non-acceptance. It is the responsibility of the sponsor to arrange for the main REC to be provided with a copy of the notice for information.

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

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Further information or clarification from the applicant

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

5.47 If time allows, however, the REC may invite the Chief Investigator to provide further information or clarification in writing by a specified date within the period of 35 days allowed for the review. If the further information is not provided by this date, or is incomplete or unsatisfactory, the amendment should be rejected.

5.48 The applicant may be invited to submit a modified amendment taking account of the REC's concerns. The members present at the meeting may delegate responsibility to the Chair to give a favourable opinion of the amendment if it is subsequently modified in a way that meets all the concerns of the REC. Procedures for reviewing modified amendments are set out in paragraph 5.50-5.54.

5.49 Where it appears that the amendment may significantly affect the scientific value of the trial, for example because it modifies the recruitment targets, the selection criteria or the data analysis, the REC may require that the applicant provides evidence of further scientific review in support of the amendment.

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Modified amendments

5.50 Where the REC gives an unfavourable opinion of a substantial amendment, the Chief Investigator may submit a modified amendment taking account of the Committee's concerns. The notice of amendment form should be re-submitted, amended as necessary, and should be accompanied by any supporting documents that have been modified. The form should be clearly marked to indicate that it relates to a modified amendment.

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

5.52 The Co-ordinator should make arrangements for a modified amendment to be reviewed as soon as possible. It should be reviewed at a sub-committee meeting or, if authority has previously been delegated under paragraph 5.48, by the Chair. The REC should decide to give either a favourable or unfavourable opinion. The Co-ordinator should notify the sponsor and Chief Investigator of the decision of the REC within 14 days of the receipt of the modified amendment, using either SL34 (favourable opinion) or SL35 (unfavourable opinion). In the case of CTIMPs a copy of the opinion letter should be sent by email to clintrialhelpline@mhra.gsi.gov.uk (see footnote to paragraph 3.63E).

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

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

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Appeals

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

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Amendments requiring submission of a new application

5.56 Where a proposed amendment would fundamentally alter the nature of the research and the extent of the involvement of, or risk to, existing and/or potential participants, the REC may give an unfavourable opinion and instead request submission of a new application for full ethical review. Examples might be where the proposed amendment involves:

- A change in the primary purpose or objective of the research, such as introduction of additional genetic studies.
- A substantial change in research methodology.
- Introduction of new classes of investigations or other interventions (rather than simply re-scheduling or modifying those already approved).
- Recruitment of a new type of participant (especially if these would be regarded as being from vulnerable groups).

5.57 Amendments involving the submission of a separate protocol should always require the submission of a new application.

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Amendments to multi-site studies

5.58 In general there is no requirement for other RECs to be informed of protocol amendments to multi-site studies. In most cases, protocol amendments will not have significant ethical implications for the suitability of individual sites to conduct the study. (For amendments relating to particular sites, see paragraphs 5.62-5.74.)

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

5.60 Where, exceptionally, the main REC considers that the proposed changes to the study could have significant ethical implications for the suitability of sites, it should first consider the guidance in paragraph 5.56. It may well be that a new application is required for the study as a whole in such cases.

5.61 Where the main REC considers it reasonable to give a favourable opinion on the amendment without a new application, but remains concerned about possible ethical implications at individual sites, it should proceed as follows:

- The favourable opinion should be issued to the applicant within 35 days.

- New SSAs should not be requested before issuing the opinion, as the 35 day time limit allows insufficient time for this process.
- The main REC should consider attaching conditions to a favourable ethical opinion, relating to implementation at local sites. For example, the opinion might be given on the assumption that the amendment will not be implemented at any site lacking the appropriate facilities, or that any additional support required by participants will be provided locally. The sponsor or Chief Investigator could also be required to send a copy of the opinion letter to the care organisation responsible for research governance at the site. The responsibility would then lie with the sponsor and the care organisation to ensure that it was reasonable for the amendment to be implemented.
- Exceptionally, the main REC may also write directly to SSA RECs by letter or e-mail, explaining the specific concerns of the main REC about the potential local implications of the amendment. (A copy of the amendment should be enclosed, or the main REC may summarise the relevant points.) This may be for information only, or RECs may be asked to review a particular aspect of the SSA and to advise the main REC by a specified date whether it has any concerns about the continued suitability of the site.
- The Chair of the REC should consider any such request and respond in writing on behalf of the REC. Other members may be consulted if appropriate. Further information may be sought from the Principal Investigator.
- In the light of any site-specific objections raised by a REC, the main REC may review the favourable opinion for a site at any time (see paragraph 9.78-9.84).

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Amendments relating to individual sites

Inclusion of new sites requiring SSA

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

- In all cases the Chief Investigator should arrange for the Principal Investigator to apply for SSA according to normal procedure.
- The SSA REC Co-ordinator should validate the application for SSA in the normal way. The main REC will be notified by RED that a valid application has been received.
- In the case of a CTIMP, the sponsor (or sponsor's representative) should *also* send the European Commission notice of amendment form to the main REC, giving the name and address of the new site and Principal Investigator. *This additional requirement only applies where the site was not included in the list of proposed trial sites in the original REC application and request for authorisation to the MHRA (see paragraph 5.63).* Sites already notified to the main REC and MHRA may be added by submitting SSA only.
- In the case of a non-CTIMP, there is no requirement for the Chief Investigator to submit a notice of amendment form to the main REC. All sites may be added by submitting SSA only.
- In all cases, the 35 day time period for the review begins when a valid application for SSA is received by the SSA REC. The outcome of the SSA should be notified to the main REC within 25 days of the receipt of the application.
- The main REC should issue the opinion for the new site within 35 days by issuing SL21 (with an updated version of SF1) or SL22. A copy should be sent to the sponsor.

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

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Exemption from SSA

5.64 In the case of studies designated as "SSA-exempt" (see paragraph 4.20), the inclusion of an additional site is not a substantial amendment and does not need to

be notified to, or approved by, the main REC. It is sufficient for information on the number of sites taking part in the study to be included in the annual progress report.

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

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Extension to additional domains

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

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

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Adults with incapacity in Scotland

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

from Scotland A REC should be provided to the applicant with the favourable opinion letter.

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Appointment of a new Principal Investigator at a site

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

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

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Redefinition of research sites

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

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Site-specific amendments to the protocol or participant information

5.72 In multi-site studies it may be necessary for site-specific amendments to be made to the research procedures in the protocol or to study documentation such as the participant information sheet. Where such amendments meet the criteria for minor amendments (see paragraph 5.34), the sponsor may authorise the amendment without notifying the main REC or seeking an ethical opinion. For example, the generic participant information sheet will normally be customised to give local contact numbers and information about complaints procedures and, where applicable, independent advisers.

5.73 Where a site-specific amendment is substantial, a notice of amendment form should be submitted to the main REC for review according to normal procedure. Guidance on the consideration of site-specific issues is given in paragraph 5.61.

5.74 Where significant local variations in protocol procedures or information for participants can be expected at the outset, the sponsor and Chief Investigator should reflect these as far as possible in the main REC application. For example, the protocol may allow a choice of comparator regimes or variation in standard radiation dose, depending on normal clinical practice at each site. Where appropriate, the generic participant information sheet may include text options to be selected by the local Principal Investigator, depending on local practice. The main REC should then consider whether such variation is permitted within the terms of the single ethical opinion for the study.

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Appointment of a new Chief Investigator

5.75 The appointment of a new Chief Investigator is a substantial amendment, requiring a favourable opinion from the main REC. In addition to the notice of amendment, the applicant should submit:

- A copy of the new Chief Investigator's CV
- The Declaration sheet at Part B Section 7 of the application form, signed by the new Chief Investigator.

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

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Absence of Chief or Principal Investigator

5.77 From time to time, Chief Investigators or local Principal Investigators may be absent due to annual leave, sick leave, maternity leave, sabbatical or for other reasons. For short absences, the CI or PI is responsible for arranging adequate cover. Where this has not been possible, for example because the absence was unforeseen, the research sponsor will be responsible for ensuring that appropriate arrangements are made for the continued conduct of the study. The care organisation hosting the research is normally responsible for monitoring the conduct of the study.

5.78 In some cases it may be necessary to appoint an acting or new CI or PI. The following guidance may be given to CIs, PIs and sponsors:

- Where the absence is likely to exceed 3 months or is indefinite, it is recommended that an acting or new CI or PI should be appointed. An application for SSA should be submitted and processed in the normal way.
- Where the absence is likely to exceed 4 weeks but will be less than 3 months, it may not be necessary to appoint an acting CI or PI but a letter may be sent to the main REC for information explaining what cover arrangements are being made. (In the case of an acting PI, the letter should be copied to the SSA REC and the care organisation. The SSA REC should notify the main REC if it has any concerns about the suitability of the arrangements.) The main REC has the discretion to request formal appointment of an acting CI or PI.
- For absences shorter than 4 weeks, it is not generally necessary to notify the main REC or SSA REC.

5.79 The above guidance is not prescriptive. Other factors may need to be weighed, such as the nature, duration and progress of the research, the rate of recruitment and the structure of the research team.

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Urgent safety measures

5.80 The sponsor, Chief Investigator or any Principal Investigator may make changes to the conduct of a study for urgent safety-related reasons without first giving notice to the REC or obtaining a favourable opinion. Procedures relating to urgent safety measures are described in paragraph 9.20-9.23.

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Section 6: Sub-committees

Summary

Sub-committees consist of members of the Research Ethics Committee appointed to carry out functions delegated by the full REC. The decisions of a sub-committee do not need to be ratified by the full committee, unless an issue is specifically referred for further consideration.

Section 6 gives full guidance on the functions of sub-committees. In summary these are:

- Considering further information provided by applicants and advice from referees; and confirming the final opinion of the Committee on new applications
- Reviewing amendments and modified amendments
- Monitoring the safety and progress of research with a favourable opinion
- Site-specific assessments.

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

The REC can set up a "standing sub-committee" or appoint sub-committees on an *ad hoc* basis. The Chair should ensure that relevant expertise is available.

A standing sub-committee must consist of at least two committee members, including the Chair or vice-Chair, who can attend meetings or submit written comments regularly. Normally at least four members should be appointed to allow for absences.

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

Deputy members may attend in place of their lead member but should not be appointed as members of a sub-committee in their own right. One member may be co-opted from another REC at any sub-committee meeting.

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

Procedures relating to the submission of written comments, referees, attendance of investigators and observers are essentially the same as for meetings of the full Committee.

Guidance is given on the responsibilities of the Co-ordinator. These are essentially the same as for meetings of the Committee, except that:

- Papers should normally be distributed no later than 3 days before the meeting.
- Minutes of telephone meetings should be taken by the Chair if the Co-ordinator cannot follow the discussion using conference facilities.
- Decisions taken at a sub-committee meeting should be reported to the full Committee in the Co-ordinator's report, or the minutes may be attached to the report.

Section 6 Sub-committees

Statutory provisions

6.1 The Clinical Trials Regulations generally provide for the exercise of any of the REC's functions by a sub-committee consisting of members of the Committee.

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Functions of sub-committees

6.2 The general guidance from NRES Head Office is that the functions set out in paragraph 6.3 should normally be exercised by a sub-committee of the REC.

6.3 Sub-committees may exercise the following functions on behalf of the REC:

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

(ii) Review of notices of amendment and modified amendments relating to an application to which the REC has given a favourable opinion (see Section 5).

(iii) Monitoring of research studies to which the REC has given a favourable opinion (see Section 9), including:

- Review of annual progress reports, notifications of the conclusion of the trial or reports of early termination, and final study reports
- Review of urgent safety measures taken by the sponsor
- Review of quarterly or annual safety reports together with lists of SUSARs or SSARs (in the case of CTIMPs)
- Review of serious adverse events (in the case of other research)
- Review of any other safety reports.

(iv) Site-specific assessments (see Section 4).

6.4 A sub-committee should not undertake the primary review of a new application for ethical review. Applications should be considered at a quorate meeting of the full Committee prior to any further consideration by a sub-committee.

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

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Authority of sub-committees

6.6 A sub-committee has delegated authority to take decisions on behalf of the REC on the matters listed in paragraph 6.3 above. Decisions taken by the sub-committee should not require ratification at the Committee meeting, unless the sub-committee specifically decides to refer a matter for further consideration and decision by the Committee. Decisions made by a sub-committee on behalf of the REC cannot be subsequently reversed by the REC.

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Establishment of sub-committees

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

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

(i) A standing sub-committee may be established. This should consist of at least two members who would be able to attend meetings or submit written comments on a regular basis. It is suggested that at least four members should normally be appointed to allow for absences. The membership should include at least the Chair and/or vice-Chair. Other members may be invited to