Duration of a favourable ethical opinion

9.10 The favourable ethical opinion of the main REC applies for the duration of the research, except where action is taken to suspend or terminate the opinion (see paragraph 9.78-9.84). Where the duration of the study is to be extended beyond the period specified in the application form, the main REC should be notified for information by letter, giving reasons for the extra time needed to complete the research. (Annual progress reports should continue to be submitted if the study duration is extended in this way – see paragraphs 9.10-9.19.) Extension of the study period is not in itself a substantial amendment, except where it is related to other amendments that would be substantial, such as an increase in target recruitment, addition of new procedures or extension of follow-up. It is not necessary to obtain formal approval for extension of the study period, though the main REC may review its favourable opinion of the study at any time (see paragraph 9.78-9.84).

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Progress reports

9.11 Progress reports on all research with a favourable opinion should be submitted to the main REC at least annually. The first annual report should be submitted 12 months after the date on which the favourable ethical opinion was given. Reports should continue to be submitted at least annually until the end of the study is notified, except where paragraph 9.19 applies.

9.12 When giving a favourable opinion on an application, the main REC may require as an approval condition that more regular reports should be submitted, or it may request an additional progress report at any time.

9.13 Progress reports should be in the format prescribed by NRES and published on the website. Reports may be submitted by the sponsor or the Chief Investigator, but should always be signed by the Chief Investigator.

9.14 Progress reports should be acknowledged by the Co-ordinator (SL37 may be used) and reviewed at least by the Chair or, at the Chair's discretion, by one or more

members of the Committee (for example, the lead reviewer for the study) or a Scientific Officer. The Committee should be notified of the receipt of the report (see paragraph 2.15). Copies or summaries may be distributed to members.

9.15 It is not necessary for the main REC to re-confirm the favourable ethical opinion for the study each time a progress report is received. The presumption is that the opinion remains valid for the duration of the study, unless the REC has grounds for review.

9.16 Where the Chair or another member, or a Scientific Officer, considers that the progress report gives grounds for reconsidering the REC's opinion on the research, the matter should be considered at a meeting of the Committee or sub-committee. Where it is proposed to suspend or terminate the REC's favourable ethical opinion, the matter should be considered at a meeting of the REC (see paragraph 9.81).

9.17 Where a progress report is not received by the due date, the REC Co-ordinator should send the reminder SL38. If the report is still not received after a further period of one month, the Chair should consider what further action should be taken. Where it is proposed to suspend the REC's favourable ethical opinion, the matter should be considered at a meeting of the REC (see paragraph 9.81).

9.18 In the case of multi-site studies, there is no requirement for copies of progress reports to be sent to relevant local RECs by the sponsor or Chief Investigator. Nor is there any requirement for local Principal Investigators to submit progress reports on the local conduct of the research to the relevant local REC, unless exceptionally the local REC considers this is necessary to monitor local issues relating to the suitability of the site.

9.19 Following receipt of the first progress report, the Chair of the main REC has the discretion to waive the requirement for further reports on receipt of a written request from the Chief Investigator. This might be appropriate where a study has completed recruitment and intervention, but has a long period of follow-up with minimal involvement of participants.

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Urgent safety measures

9.20 The Clinical Trials Regulations provide that the sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect the subjects of a CTIMP against any immediate hazard to their health or safety. The main REC and the MHRA must be notified immediately and in any event within 3 days that such measures have been taken and the reasons why. The policy from NRES Head Office is that these requirements should apply to all other research with a favourable opinion from a REC.

9.21 The initial notification to the REC should be by telephone. Notice in writing should be sent within 3 days. The notice should set out the reasons for the urgent safety measures and the plan for further action.

9.22 Notifications of urgent safety measures should be reviewed at a meeting of the main REC or sub-committee. The REC should consider whether the measures taken are appropriate in relation to the apparent risk to participants, and what further action the sponsor and investigator(s) propose to take, for example the submission of amendments to the protocol. Where any concern arises about the safety or welfare of participants or the conduct of the research, the REC should address these with the sponsor or Chief Investigator in writing.

9.23 Where urgent safety measures are taken by a Principal Investigator, the main REC should ensure that the relevant local REC is informed and should seek its advice if any concern arises about the continued suitability of the site.

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Safety reporting in clinical trials of investigational medicinal products

European Commission guidance

9.24 Under the EU Directive the European Commission has issued "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" (ENTR/CT3). The guidance describes the requirements to be followed by sponsors for safety reporting both to the

competent authority and the ethics committee in each member state. This document is the main source of guidance for sponsors of CTIMPs in the UK. The following paragraphs summarise the key requirements.

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Expedited reporting of individual SUSARs in the UK

9.25 Suspected Unexpected Serious Adverse Reactions (SUSARs), which are associated with the use of an investigational medicinal product (IMP) in the trial, must be notified both to the MHRA and to the main REC in accordance with the requirements of the Directive for expedited reporting. This includes SUSARs associated with an active comparator drug used in the trial. **In the case of the main REC, the sponsor is only required to report in expedited fashion SUSARs occurring in the concerned trial in the UK.** SUSARs occurring in the trial outside the UK are subject to expedited reporting to all relevant competent authorities, but do not need to be notified in this way to ethics committees in the UK. They should however be included in periodic line listings (see paragraphs 9.38-9.41). Where RECs receive expedited reports of non-UK SUSARs, the Co-ordinator may arrange for them to be shredded and there is no requirement to acknowledge receipt.

9.26 In addition, for IMPs without a marketing authorisation in any Member State, other SUSARs associated with the IMP are subject to expedited reporting. This includes SUSARs occurring in another trial conducted by the same sponsor, or which come to the attention of the sponsor from another source. The main REC will only receive such reports where the SUSAR occurs in the UK.

9.27 A serious adverse reaction is an untoward and unintended response to an IMP at any dose, that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect.

9.28 An adverse reaction is considered to be "unexpected" if its nature and severity are not consistent with the information about the medicinal product set out in the trial documentation.

9.29 A SUSAR which is *fatal or life-threatening* must be reported to the MHRA and the main REC as soon as possible and in any event within 7 days after the sponsor became aware of the event. Any additional relevant information must be reported within 8 days of sending the first report.

9.30 A SUSAR which is *not fatal or life-threatening* must be reported to the MHRA and the main REC as soon as possible and in any event within 15 days after the sponsor first became aware of the event.

9.31 An adverse event associated with placebo will not normally satisfy the criteria for a SUSAR. If this occurred exceptionally it should be reported.

9.32 Sponsors must also report to all investigators concerned any findings that could adversely affect the safety of study subjects. It may do so by means of periodic line listings of SUSARs, accompanied by a summary of the evolving safety profile.

9.33 There is no requirement to provide reports to RECs other than the main REC. Sponsors should not send reports to other RECs. Where they do so, the Co-ordinator may arrange for the reports to be shredded and there is no requirement to acknowledge receipt. (See paragraph 10.10 for guidance on the designation of the main REC in trials approved by ethics committees prior to 1 May 2004.)

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Other expedited safety reports

9.34 The European Commission guidance recommends that expedited reports on the following occurrences should also be sent to the competent authority and the main REC within 15 days:

(a) an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important

(b) post-study SUSARs that occur after the patient has completed a trial and are reported by the investigator to the sponsor

(c) a new event, related to the conduct of the trial or the development of the IMP, that is likely to affect the safety of subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial (for example a SAE occurring during the run-in period)
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity).
- any anticipated end or temporary halt of a trial for safety reasons where the trial is conducted with the same IMP by the same sponsor in another country.

(d) the conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects.

9.35 The MHRA recommends expedited reporting both to MHRA and the main REC of any information that materially alters the current risk/benefit assessment of the IMP or merits changes in the way the IMP is administered or the overall conduct of the trial.

9.36 It is not generally required to notify serious adverse events occurring in the trial not meeting the criteria for SUSARs, other than under paragraph 9.34(d) above.

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Unblinding of reports

9.37 In the case of double-blinded trials, the European Commission guidance recommends that reports of SUSARs should normally be unblinded. So far as the UK is concerned, the MHRA normally requires treatment codes to be broken but advises that the blind should be maintained for persons responsible for the analysis and interpretation of results, e.g. the Data Monitoring Committee, and for staff working on separate trials. Waivers may be applied with the agreement of the MHRA.

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Periodic safety reports

9.38 For each IMP being tested in the trial, the sponsor should provide the main REC with an annual report on the safety of subjects in all clinical trials of the product for which the sponsor is responsible, whether in the UK or elsewhere. The report, which should be no longer than 10 pages excluding line listings, should:

- give a concise description and analysis of all new and relevant findings that could have a significant impact on the trial population
- analyse the safety profile of the IMP and its implications for subjects' exposure, taking into account all safety data including drop-outs for safety reasons
- take into account supporting results of non-clinical studies or other experience with the IMP that are likely to affect the subjects' safety
- provide an updated risk-benefit evaluation for the trial
- describe any measures taken or proposed to minimise risks
- consider the need to amend or update the protocol, participant information sheet, consent form and investigator brochure.

9.38A Annual reports should be accompanied by a line listing of all Suspected Serious Adverse Reactions (SSARs) occurring in relevant trials during the year, including both expected and unexpected reactions. Line listings should include SSARs occurring in other EU member states or worldwide, as well as those in the UK.

9.39 Where a commercial sponsor is conducting the trial or any other trials of the IMP outside the UK, it should also provide the main REC with 6 monthly safety reports as recommended by the European Commission in paragraph 5.1.6.5 of ENTR/CT3). Six monthly reports should include a global line listing of all SUSARs occurring in relevant trials during the reporting period, together with a brief report highlighting the main points of concern. This reporting mechanism meets the obligations of the sponsor under the Directive to report non-UK SUSARs to the ethics committee. Non-commercial sponsors are only required to provide annual safety reports.

9.40 If a sponsor is conducting several CTIMPs in the UK with the same IMP, one safety report may be prepared covering all relevant trials. The report should be sent to each main REC concerned. A separate cover sheet should normally be submitted for each trial (see paragraph 9.48).

9.41 Periodic reports should be sent to the main REC as soon as practicable after the end of the reporting period, and within 60 days at the latest. It is not necessary to send copies of periodic reports to other RECs.

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Reporting timeframe for periodic reports

9.42 The reporting timeframe for periodic reports starts with the date of the first authorisation of the trial by a competent authority in any Member State of the European Economic Area. It is not defined in relation to the date on which the main REC gave a favourable opinion for the trial.

9.43 For UK-only clinical trials that commenced before 1 May 2004, the reporting period starts with the issue date of the CTX letter or first DDX exemption letter by the MHRA (or previously by the Medicines Control Agency).

9.44 Where the report covers more than one clinical trial, the reporting period starts on the date on which the first of these trials was authorised in any Member State.

9.45 If the sponsor is the marketing authorisation holder of the tested IMP, the reporting period starts with the International Birth Date (IBD). If the IMP is granted a marketing authorisation for the first time in any Member State while it is being tested in a clinical trial, the reporting period would change from the first date of authorisation to the IBD.

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Format of safety reports

9.46 Sponsors may adopt their own format both for expedited reports and periodic safety reports provided that the basic information set out in the European Commission guidance is included. Reports of SUSARs will normally be in the CIOMS-1 format (available at http://www.cioms.ch) that is widely accepted as the standard within the pharmaceutical industry. The required data elements for SUSAR reports and line listings are set out respectively in Annexes 3 and 4 to ENTR/CT3. A causality

assessment should be included in all case reports, including assessments from both sponsor and investigator if there is no agreement.

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Submission of safety reports

9.47 Expedited and periodic safety reports will normally be submitted by the sponsor, but may also be submitted by the sponsor's legal representative or the Chief Investigator for the study. Initial notifications of SUSARs may be made by fax, e-mail or telephone. Follow-up reports and all other safety reports should be sent to the REC office by post. Three copies should be provided of all enclosures, except for SUSAR reports (one copy only). Extensive line listings may be submitted on CD (three copies of the CD should be provided).

9.48 Each submission to the main REC should be accompanied by the Safety Report form for CTIMPs, which is a standard cover sheet published on the NRES website. The form should be signed in ink. A single form may be used for the submission of several safety reports relating to the same trial. The form should specify the trial concerned and enclosures should be individually listed and referenced. Reports should not normally cover more than one trial. However, the REC may permit this where two trials are very closely connected, for example a main study and an extension study with the same treatment regime.

9.49 The Co-ordinator should acknowledge receipt of all written reports within 30 days by signing and returning a copy of the form to the person making the submission. The form should not be copied to investigators in the case of double-blind trials as this may compromise the blind.

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Responsibilities for monitoring the safety of clinical trials

9.50 The primary responsibility for monitoring the safety of research participants lies with the trial sponsor. For certain kinds of CTIMP – trials with predicted high morbidity or mortality, or double-blind trials with unknown or uncertain risks - sponsors are strongly encouraged by the Commission guidance to establish an independent Data

Monitoring Committee to advise on safety issues. The sponsor has a duty to take action, which may include urgent safety measures, protocol amendments or even the suspension or termination of a trial, where the safety profile or the risk/benefit analysis changes significantly.

9.51 Sponsors are required to submit complete data on all SUSARs occurring in EU member states to the Eudravigilance CT module of the European Clinical Trials Database (EudraCT), as well as other specified safety data. This enables the relevant competent authorities, in collaboration where necessary, to maintain an effective overview of the safety issues in a clinical trial. In the UK regulatory context, the MHRA will actively monitor the safety of clinical trials through its access to the European databases. Where the MHRA raises safety concerns with the sponsor, it will directly inform the main REC so that any implications for the ethics of the trial can be considered in parallel.

9.52 In this context, the responsibilities of the REC are inevitably more limited. RECs do not have access to comprehensive safety data (in particular, SUSARs outside the UK are not subject to expedited reporting to the REC), nor do they generally have the resources and expertise required to carry out in-depth analysis of the available data. The REC should, however, be ready to act on safety concerns that are brought to its attention by the sponsor or the MHRA. In particular, the REC is responsible for ensuring that the consent of participants continues to be based on accurate and up-to-date information about risks and benefits.

9.53 The main REC should therefore review safety reports in accordance with the following guidance.

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Review of safety reports by the main REC

9.54 Expedited reports of SUSARs or other occurrences should be acknowledged and filed by the Co-ordinator. They do not need to be seen by the Chair. There is no requirement for the Committee to be notified routinely of the receipt of expedited reports, or for any review to be carried out, as the overall safety of the trial cannot be assessed on the basis of such limited data. Reference may subsequently be made to

reports of SUSARs where an expert member or referee considers that this may be useful in the context of safety reports about the trial as a whole.

9.55 Periodic safety reports should be reviewed at least by the Chair and, unless the Chair has appropriate expertise, by an expert member or referee. The latter should normally be a clinical pharmacologist, a trial pharmacist or a specialist in the disease field. The review may take place in correspondence or at a sub-committee or Committee meeting. The review may be confined to the summary of safety issues. The REC is not required to make a detailed assessment of line listings. The purpose of the review is to:

- Check the accuracy of the risk/benefit analysis as described in the patient information sheet
- Consider the possible need for new information to be given to patients and their consent sought to continue in the study
- Consider any other issue that may be relevant to the ethics of the trial.

9.56 Where concerns arise about any of the above, the REC may write to the Chief Investigator or sponsor to express its concerns, and may request further information. The correspondence should be copied to the Head of the Clinical Trials Unit at the MHRA by email (see paragraph 3.63). The Chief Investigator may be requested to attend a meeting of the sub-committee or Committee to discuss the concerns of the REC.

9.57 Where findings and recommendations from Data Monitoring Committees are received by the main REC (see paragraph 9.35), they should be reviewed in the same way as periodic safety reports.

9.58 The Committee should be notified in the Co-ordinator's report (see paragraph 2.15) of the receipt of periodic safety reports and recommendations from Data Monitoring Committees. The report should state who has reviewed the safety reports, and summarise any concerns that have arisen and the further action taken. Where appropriate, the concerns may be discussed at a meeting of the Committee.

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Communications with MHRA on safety issues

9.58A The main REC should draw the attention of the MHRA to any substantial concerns about the safety of trial subjects, the accuracy of the risk/benefit analysis or the need for new information to be given to subjects. Communications should be sent to the Head of the Clinical Trials Unit by email (see paragraph 3.63). SL16 may be used. The correspondence will be acknowledged.

9.58B Where the MHRA has concerns about the safety of trial subjects or there is a change in the risk/benefit analysis, it will keep the main REC informed of any action it takes. The Head of CTU will ensure that any relevant correspondence with the sponsor is copied to the main REC. The main REC may seek further information or clarification from the Head of CTU by email or telephone. It may also recommend that the CTU takes action in relation to the CTA, for example to request amendment of the participant information sheet.

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Safety reporting for other research

9.59 In research other than CTIMPs, a Serious Adverse Event (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

9.60 An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

9.61 Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the NRES website.

9.62 The Chief Investigator should include a report on the safety of participants in the annual progress report.

9.63 Individual reports of SAEs should be reviewed at a sub-committee or Committee meeting.

9.64 There is no requirement to provide reports to RECs other than the main REC.

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Protocol deviations

9.65 It is generally considered acceptable for a sponsor or Chief Investigator to make (or permit other investigators to make) minor deviations from a protocol to deal with unforeseen circumstances. Such deviations may be considered minor (or "non-substantial") amendments and do not need to be routinely notified to the main REC. However, if the deviation would meet the criteria for a "substantial amendment" it should be notified to the main REC and an ethical opinion sought. In particular, where the deviation is made to protect a subject from an immediate hazard to their health or safety, this should be notified to the main REC as an urgent safety measure and reviewed accordingly (paragraphs 9.20-9.23).

9.66 Where the deviation is necessary due to errors or inadequacies in the protocol, the sponsor is responsible for making appropriate amendments. If the amendments are substantial, they should be submitted to the main REC for ethical review before they are implemented (see Section 5). There is no provision in the Regulations for ethics committees to give an opinion on proposed deviations relating to individual participants (for example, to waive the eligibility criteria for a particular participant). RECs should not review such proposals except where the sponsor notifies a substantial amendment relating to the general conduct of the trial.

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Breaches of the protocol or good clinical practice

9.67 A distinction should be made between "minor protocol deviations", which are agreed with the sponsor or Chief Investigator either in advance or as soon as possible after the event, and "serious breaches of the protocol or GCP", which are made without permission as a result of error or fraud/misconduct.

9.68 The main REC should be notified of serious breaches of the protocol or of the conditions or principles of Good Clinical Practice (GCP) as set out in the Regulations. A breach of the protocol or GCP is "serious" if it is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the trial. Where this applies, the sponsor should notify the main REC and the MHRA within 7 days of the matter coming to their attention. The report to the main REC should give details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given and the main REC informed what further action the sponsor plans to take. Any such report should be considered at a meeting of the Committee or sub-committee. Where consideration is given to reviewing the opinion, either for the whole of the UK or at an individual site, the REC should follow the guidance in paragraphs 9.78-9.84. The matter should be reported to the OREC Manager and appointing authority in line with the guidance in paragraphs 9.89-9.91 and 9.97.

9.69 Where information about a serious breach of the protocol or GCP comes to the attention of the local REC for a research site, this should be reported to the main REC.

9.70 There is no requirement to notify minor breaches of the protocol GCP not meeting the criteria in paragraph 9.68.

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Declaration of the conclusion or early termination of the research

9.71 The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the main REC in writing that a CTIMP has ended within 90 days of the conclusion of the research.

9.72 If the trial is terminated early, the sponsor should notify the main REC within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.73 The definition of the conclusion of the research should be provided in the protocol and any change to this definition should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol.

9.74 Declarations of the conclusion or early termination of a CTIMP should be in the form prescribed by the European Commission at Annex C to 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 the trial" (ENTR/CT1).

9.75 The policy from NRES Head Office is that the requirement to notify the main REC of conclusion or early termination should also apply to all other research with a favourable opinion. In the case of non-CTIMPs, reports should be submitted in the form prescribed by NRES and published on the website.

9.76 All notifications of the conclusion or early termination of a study should be acknowledged by the Co-ordinator (SL39 may be used) and reviewed by the Chair or, at the Chair's discretion, by another member of the Committee or a Scientific Officer. The Committee should be notified in the Co-ordinator's report. No further action is required unless the Chair considers that issues are raised requiring discussion at a meeting of the REC or sub-committee.

9.77 In general there is no requirement to submit an annual safety report or annual progress report with a declaration of conclusion or early termination. However, in the case of research lasting less than 12 months the REC has the discretion to request a final safety report

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Review of a favourable ethical opinion

9.78 The main REC may review its favourable ethical opinion of a study at any time. In particular, this might be prompted by safety reports, progress reports or any other information received about the conduct of the study. The Chief Investigator or sponsor may ask the main REC to review its opinion, or seek advice from the REC on any ethical issue relating to the study.

Suspension or termination of opinion on a non-CTIMP

9.79 A favourable ethical opinion on a non-CTIMP may be suspended or terminated by the main REC due to serious concern about one of the following:

(a) The scientific validity of the study
(b) The health or safety of participants
(c) The competence or conduct of the investigator(s)
(d) Serious or repeated breach of approval conditions
(e) A delay of at least 2 years in the commencement of the study leading to doubts about the continuing validity of the ethical opinion given on the original application
(f) The adequacy of the site or facilities
(g) Suspension or termination of regulatory approval for the study.

9.80 In the case of multi-site studies, the favourable ethical opinion for a particular site may be suspended or terminated by the main REC following new information received from the site-specific assessor or another source about the suitability of the site (see paragraph 4.84). The favourable opinion could continue to apply to other trial sites in these circumstances.

9.81 A decision by the REC to suspend or terminate a favourable ethical opinion should be taken only at a quorate meeting of the full Committee. Before taking this course the REC should weigh carefully the implications for any research participants already recruited. The Chief Investigator should be notified of the decision by the Chair using SL42. The letter should specify the following:

- whether the opinion is suspended or terminated
- the reasons for the suspension or termination
- the date from which the suspension or termination applies
- any action necessary to inform patients or arrange for their continuing treatment outside the trial protocol

and, in the case of suspension,

- any conditions which are to be satisfied before the favourable opinion may be re-confirmed, either generally or at a particular site.

9.82 A copy of the letter should be sent to the sponsor and, in the case of single-site studies, the care organisation. In the case of a multi-site study, it is the responsibility of the Chief Investigator or the sponsor to ensure that other investigators, local collaborators and care organisations are informed. Where the opinion is suspended or terminated at a particular site, a copy of the letter should be sent to the Chair of the relevant local REC, and the action taken in relation to the site should be noted on form SF1.

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Review of opinion on a CTIMP

9.83 Under the Clinical Trials Regulations, the decision to suspend or terminate the CTA and therefore to halt the trial lies solely with the MHRA. *The ethics committee has no power under the Regulations to suspend or terminate the CTA or legally withdraw the ethical opinion given previously*. However, the main REC may review its opinion in the light of new ethical concerns following any new information received about the trial. It may also notify the MHRA that it no longer has a favourable opinion of the trial. Any such notification should be based on a decision taken at a quorate meeting of the full committee.

9.83A Where the main REC decides that it no longer has a favourable opinion of a trial, the Chair should write to the Head of the Clinical Trials Unit by email explaining its concerns in full. SL16 may be used. The REC may recommend that consideration is

given to suspending or terminating the CTA. Any such recommendation should relate to serious concern about one or more of the following:

(a) The scientific validity of the trial
(b) The health or safety of participants
(c) The competence or conduct of the investigator(s)
(d) A delay of at least 2 years in the commencement of the trial leading to doubts about the continuing validity of the ethical opinion given on the original application
(e) The adequacy of the site or facilities.

The CTU will consider what action should be taken in relation to the CTA and will notify the main REC accordingly. The action taken could include request to the sponsor for further information, request for amendment of the trial, or suspension or termination of the CTA. Further information or clarification may be sought from the main REC about its concerns. The CTU may seek separate advice from referees.

9.84 The MHRA will directly inform the main REC where it suspends or terminates the CTA (which will automatically halt the trial), and also where it re-instates a CTA following suspension. The main REC should consider whether the suspension or termination has any implications for the welfare and safety of patients. The sponsor or Chief Investigator may be requested to provide further information about the steps being taken to inform patients or arrange for their continuing treatment outside the trial protocol. The MHRA should be kept informed of any action taken by the main REC.

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Further reporting after the conclusion of the trial

9.85 If after the conclusion or early termination of a trial the risk/benefit analysis is considered to have changed, the sponsor or Chief Investigator should notify the main REC in case this affects the planned follow-up of trial participants. The plan for further action to inform or protect participants should be described.

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Final reports

9.86 A summary of the final report on the research should be submitted to the main REC within one year of the conclusion of the research. This applies to both CTIMPs and all other research. There is no standard format for final reports. As a minimum, the main REC should receive 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.

9.87 All such reports should be acknowledged by the Co-ordinator (SL40 may be used) and reviewed by the Chair or, at the Chair's discretion, by another member of the Committee or a Scientific Officer. The Committee should be notified of the receipt of the report in the Co-ordinator's report. At the discretion of the Chair, copies or summaries may be distributed to members. No further action is required unless the Chair considers that issues are raised requiring discussion at a meeting of the REC or sub-committee.

9.88 If the final report is not received within one year of the conclusion of the research, the Co-ordinator should send a reminder letter (SL41 may be used).

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Research-related fraud and misconduct – general policy

9.89 Where a REC receives information suggesting that any kind of fraud or misconduct may have occurred in relation to an application for ethical review or the conduct of research, the Chair or Co-ordinator should pass the information confidentially to the OREC Manager in writing, copied to the REC's appointing authority. If the REC concerned is not the main REC for the study, a copy should also be sent to the main REC and its OREC Manager. The OREC Manager for the REC making the report should notify the Operations Director at NRES. It will be for the Operations Director, in consultation with the OREC Manager and the appointing authority, to decide whether the information should be shared with other bodies so that the matter can be formally investigated if appropriate. Consideration should be given to notifying the following:

- The research sponsor
- The researcher's employer
- The Chief Executive and R&D Director for any relevant NHS care organisation(s)
- MHRA GCP Inspectorate *(CTIMPs only – see paragraph 9.95-9.97C)*
- MHRA (Devices) *(clinical investigations of medical devices only).*

The appointing authority and relevant RECs should be kept fully informed of any action taken.

9.90 It is for the main REC to consider whether any action needs to be taken in relation to the ethical opinion for the research, in particular where there could be an immediate risk to the safety of participants. The main REC may review the favourable ethical opinion for the study or for a particular site (see paragraph 9.78-9.84). The opinion on a non-CTIMP may be suspended pending the outcome of further investigation by other bodies. Such a decision should only be taken after careful consideration of the implications for research participants already recruited.

9.91 A member of a REC who becomes aware of possible fraud or misconduct in research should report this to the Chair and Co-ordinator of the REC, who will be responsible for reporting the matter in accordance with paragraph 9.89.

9.91A Receipt of information under this section includes any report from a member of an investigator's team of alleged fraud or misconduct.

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Criminal offences

9.92 The Clinical Trials Regulations create a variety of criminal offences relating to contravention of its provisions. In particular, it is an offence to commence or conduct a CTIMP unless the trial has received both a favourable ethical opinion from a recognised REC and a Clinical Trial Authorisation. It is also an offence to implement a substantial amendment to a CTIMP without a favourable ethical opinion, or fail to provide pharmacovigilance reports, or to fail to notify the REC of urgent safety measures or the early termination or conclusion of the trial.