# RES SOPs (Version 7.5.1) Summary of Changes, August 2021

## How to use this document

This summary of changes document includes all of the revision from version 7.4 to version 7.5.1 of the Research Ethics Service Standard Operating Procedures (RES SOPs). The left-hand column shows the wording which was present in version 7.4 and deletions are indicated by ~~strikethrough~~. The right-hand column shows the wording which is now present in version 7.5.1 and additional text is indicated by underline.

| General revisions | | | |
|---|---|---|---|
| Para | SOP 7.4 | Para | SOP 7.5 |
| | References to Notice of Substantial Amendment Form have been changed to 'substantial amendment' | | |
| | References to 'Central Booking Service' have been removed. | | |
| | References to the MCA in Northern Ireland have been updated throughout the document. | | |
| | References to CE Marking have been updated to UKCA/CE UKNI/CE-marking | | |
| | References to European Commission Guidance and Member States updated. | | |
| | Deletion of the Index. | | |

| Introduction to RES SOPs | | | |
|---|---|---|---|
| | **Implementation**<br><br>~~Proportionate Review procedures will be determined by the Head of Approvals Support, taking into account the nature of research reviewed by RECs and operational considerations.~~ | | |
| 14. | **Terminology**<br><br>A guide to the terminology used in the SOPs is set out prior to Section 1. The following should be noted in particular:<br>• Responsibilities assigned in the SOPs to the "HRA Director of the Approvals Service", "Head of Approvals Operations" or "Head of Approvals Support" may be delegated to another member of staff within the UK REC service.<br>• All references in the SOPs to "the Chair" of the REC should be interpreted as referring also to the vice-Chair when acting in place of the Chair; or, if neither is available, to the alternate vice-Chair. If all three officers are unavailable, the REC's appointing authority may appoint another member of the Committee to perform the duties of the Chair until one of the other officers becomes available. When the Chair (or a vice-Chair) is in the chair, other officers resume their status as members. | 13. | **Terminology**<br><br>A guide to the terminology used in the SOPs is set out prior to Section 1. The following should be noted in particular:<br>• Responsibilities assigned in the SOPs to the "HRA Director of the Approvals Service", "Head of Approvals Operations" or "Head of Approvals Support" may be delegated to another member of staff within the UK REC service.<br>• All references in the SOPs to "the Chair" of the REC should be interpreted as referring also to the vice-Chair when acting in place of the Chair; or, if neither is available, to the alternate vice-Chair. If all three officers are unavailable, the REC's appointing authority may appoint another member of the Committee to perform the duties of the Chair until one of the other officers becomes available. When the Chair (or a vice-Chair) is in the chair, other officers resume their status as members. |

| | | | |
|---|---|---|---|
| | • References to the Approvals Officer/REC Manager should be interpreted as the equivalent role across the UK countries.<br>• The "main REC" means the REC undertaking the ethical review of an application or, in the case of research that is underway, the REC that gave a favourable opinion or its successor. ~~In the case of research studies with ethical approvals from more than one REC prior to 1 March 2004, one of the RECs should be appointed as main REC to review amendments~~ | | • References to the Approvals Officer/REC Manager should be interpreted as the equivalent role across the UK countries.<br>The "main REC" means the REC undertaking the ethical review of an application or, in the case of research that is underway, the REC that gave a favourable opinion or its successor. |

| Glossary | | | |
|---|---|---|---|
| Page | SOP 7.4 | Page | SOP 7.5 |
| | Principal Investigator (PI) - ~~The investigator responsible for the research site where the study involves specified procedures requiring site-specific assessment (SSA). There should be one PI for each research site.~~ In the case of a single-site study, the CI and the PI will normally be the same person. | | Principal Investigator (PI) - <u>The lead researcher for a research project at a particular site. Has responsibility for the conduct of the project at that site</u>. In the case of a single-site study, the CI and the PI will normally be the same person. |
| | Electronic Authorisation - Functionality provided by IRAS to allow IRAS account holders to notify that they agree with the declarations in applications generated by the system. The authorisations also act as a mechanism for verifying that the content of the applications remains unchanged from the point at which the authorisations were made. ~~While not entirely conformant to the specification for an 'Electronic Signature' the authorisation mechanism~~ | | Electronic Authorisation - Functionality provided by IRAS to allow IRAS account holders to notify that they agree with the declarations in applications generated by the system. The authorisations also act as a mechanism for verifying that the content of the applications remains unchanged from the point at which the authorisations were made. |

| | | | |
|---|---|---|---|
| | ~~provides sufficient rigour that they replace the need for a wet ink signature on applications submitted through IRAS.~~ | | |
| | ~~Main REC - The REC undertaking the ethical review of the original application, any site specific assessment in relation to the application and further ethical review or monitoring of research given a favourable ethical opinion. Where the original main REC has closed or been merged with another REC, or where opinions were given by more than one REC prior to 1 March 2004, the main REC is the REC nominated by the Head of RES.~~ | | |
| | ~~Single ethical opinion - The ethical opinion given by a REC on a research study, with application to the whole of the UK. An ethical opinion may be either favourable or unfavourable.~~ | | |
| | ~~Type 2 Recognition - New applications are no longer allocated for review by RECs with Type 2 recognition. Such recognition is only relevant for active single domain trials for which Type 2 recognised RECs previously gave a favourable opinion and continue as the main REC.~~ | | |
| | | | Complex Innovative Trials - A Complex Innovative Trial is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously. These trials are also sometimes referred to as platform, adaptive or umbrella trials. Complex Innovative Trial designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial. |

| | | | |
|---|---|---|---|
| | Substantial Amendment - Under the Directive and the Clinical Trials Regulations, an amendment to a CTIMP that must be notified to both the ethics committee and the competent authority; it requires a favourable opinion from the main REC and/or a notice of no objection from the MHRA before it can be implemented. ~~In the case of non-CTIMPs, a substantial amendment requires the issue of a favourable opinion from the main REC except where it only involves adding a new site or PI at a NHS site.~~ | | Substantial Amendment - Under the Directive and the Clinical Trials Regulations, an amendment to a CTIMP that must be notified to both the ethics committee and the competent authority; it requires a favourable opinion from the main REC and/or a notice of no objection from the MHRA before it can be implemented. |
| **Section 1: New applications for ethical review** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| 1.14 | ~~In all other cases,~~ review by a flagged REC is strongly recommended to applicants ~~and will be the preferred allocation by CBS. However, allocation decisions may take into account other factors, including:~~<br>~~• whether a timely agenda slot is available at a flagged REC,~~<br>~~• the geographical proximity of flagged RECs to the CI's professional base (potentially affecting the CI's ability to attend the REC meeting),~~<br>~~• previous review of a closely related project by a non-flagged REC,~~<br>~~• any preference expressed by the CI for review by a particular REC~~ | 1.14 | In all other cases, review by a flagged REC is strongly recommended to applicants. |
| 1.23 | The Medicines and Healthcare products Regulatory Agency (MHRA) has published guidance on the interpretation of the statutory definition of a CTIMP and a | 1.23 | The Medicines and Healthcare products Regulatory Agency (MHRA) has published guidance on the interpretation of the statutory definition of a CTIMP and a |

| | | | |
|---|---|---|---|
| | non-interventional trial (see algorithm referenced at Annex B). Where there is doubt about the classification of a trial, it is the responsibility of the Chief Investigator or sponsor to seek authoritative advice from the MHRA Clinical Trials Helpline, using the contact details on the MHRA website. (However, the REC may check directly with the MHRA ~~if necessary – see paragraph 14.10~~.) The REC should proceed with the ethical review but advise the applicant of the possible consequences if the application has been wrongly classified. The applicant may be required to provide written evidence from the MHRA as part of the single request for further information (see Section 3). Where the MHRA advises that an application submitted as a non-CTIMP is in fact a CTIMP, the application should be withdrawn and re-submitted to a recognised REC with a EudraCT number and the additional information required. Where a study is submitted as a non-CTIMP and given a favourable opinion, and it emerges later that it is in fact a CTIMP, corrective procedures are set out in paragraph 5.3 of Annex D. | | non-interventional trial (see algorithm referenced at Annex B). Where there is doubt about the classification of a trial, it is the responsibility of the Chief Investigator or sponsor to seek authoritative advice from the MHRA Clinical Trials Helpline, using the contact details on the MHRA website. (However, the REC may check directly with the MHRA by emailing **clintrialhelpline@mhra.gov.uk and** providing a copy of the Protocol.) The REC should proceed with the ethical review but advise the applicant of the possible consequences if the application has been wrongly classified. The applicant may be required to provide written evidence from the MHRA as part of the single request for further information (see Section 3). Where the MHRA advises that an application submitted as a non-CTIMP is in fact a CTIMP, the application should be withdrawn and re-submitted to a recognised REC with a EudraCT number and the additional information required. Where a study is submitted as a non-CTIMP and given a favourable opinion, and it emerges later that it is in fact a CTIMP, corrective procedures are set out in paragraph 5.3 of Annex D. |
| 1.26 | Applications originating in England which relate to social care should normally be submitted to the Social Care REC. | 1.26 | Applications originating in England which relate to social care should normally be submitted to the Social Care REC or to a REC which is flagged to review social care research. |
| ~~1.45 (i)~~ | ~~• Evidence[9] has been provided, in the case of trials with a sponsor(s) or Chief Investigator outside the NHS, that the sponsor(s) and Chief Investigator have insurance or indemnity to cover any potential liability arising from the research (see Annex G). (In the case of research~~ | 1.44 (j) | A copy of any available comments or scientific critique reports from referees or review committees should be provided with the application (if available) together with any correspondence which explains how issues raised by scientific critique have been resolved. If the applicant |

| | | | |
|---|---|---|---|
| | ~~sponsored by an NHS body or with a Chief Investigator who is employed by the NHS, NHS indemnity will usually be ensured when final management permission is given for the research.)~~ | | states that a copy of the report is not available, the application would still be valid as long as the free text box has been completed to specify how the study had been reviewed. In the case of research undertaken mainly for educational purposes, review by the academic supervisor is considered appropriate. |
| ~~1.46~~ | ~~If the sponsor representative states, either pre or post submitting the application, that they are unable to authorise the application due to being unable to confirm that all clinical trials sponsored by the sponsor, which are in active recruitment, have been registered, the following steps should be taken:~~<br>~~a) Advise the sponsor that they should request deferral of registration for any clinical trials not registered via hra.studyregistration@nhs.net.~~<br>~~b) Advise the sponsor that once the deferral has been allowed, the declaration in the application for REC review can be electronically authorised and submitted to the REC.~~<br>~~• c) If the sponsor is not willing or is unable to request a deferral of registration, the Guidance and Advice Assurance Manager should be informed via hra.studyregistration@nhs.net. If the application for REC review has been submitted at this stage, the application should be marked as validation under consideration. The Guidance and Advice Assurance Manager will record the violation on the Registration Deferral Register and write to the sponsor. The sponsor should be asked to provide formal notification in the form of a letter, signed by the~~ | | |

| | | | |
|---|---|---|---|
| | ~~sponsor representative. The sponsor should also be informed that the matter has been recorded as a violation and that, as the violation has been formally recorded, the sponsor may authorise the form on the understanding that it is not confirming that all clinical trials in active recruitment have been registered or that there is a deferral in place. The sponsor should also be informed that a favourable ethical opinion cannot be confirmed until the authorised form has been received by the REC. If an authorised form is not received within 2 months of a provisional opinion being issued, an unfavourable opinion may be issued by the REC, but the sponsor should be informed of the intention of the REC to do this before issuing the decision.~~ | | |
| ~~1.46~~ | ~~The application should then be validated and processed in the normal way. If the application form authorised by the sponsor has not been received when the REC meeting document are made available to REC members (exceptionally under these circumstances), the application may still be marked as valid and sent to the REC for ethical review in the absence of the sponsor authorisation, as long as it is accompanied by a formal notification letter which is signed by the sponsor representative (the application remains validation under consideration until the letter is received). If the sponsor does not provide a formal notification letter and has not authorised the form, then the application should be marked as invalid and removed from the meeting.~~ | | |
| ~~1.48~~ | ~~It is essential that Part A of the application form is completed in full. Where further details are requested if a~~ | | |

| | | | |
|---|---|---|---|
| | ~~particular box is ticked, these must be provided. In particular, where the applicant indicates that referees' or other scientific critique reports are not enclosed, the applicant must justify this and describe the process of scientific review. If there is no evidence to show that scientific review has taken place prior to submission, the application may be considered invalid. In the case of research undertaken mainly for educational purposes, review by the academic supervisor is considered appropriate.~~ | | |
| ~~1.49~~ | ~~Although not a formal validation criterion, it is also highly desirable that applicants provide evidence in writing that project funding has already been obtained. This is particularly important for studies that are not commercially sponsored and require significant financial support from non-NHS bodies. If the ethics application has already been made, and the funding body requires changes to the protocol, it could be necessary to submit substantial amendments or even to withdraw and re-submit the application. Guidance should be offered to applicants about this where appropriate.~~ | | |
| 1.5~~3~~ | The validation letter includes an invitation to the Chief Investigator to attend the REC meeting (see paragraphs 2.22ff). Details of the arrangements for the meeting should be inserted, including any specific information about local meeting procedures. ~~A copy of the 'RES guidance for applicants attending a REC meeting' which is published on the HRA website may be sent by email with the validation letter.~~ | 1.~~49~~ | The validation letter includes an invitation to the Chief Investigator to attend the REC meeting (see paragraphs 2.22ff). Details of the arrangements for the meeting should be inserted, including any specific information about local meeting procedures. |

| | | | |
|---|---|---|---|
| 1.7~~8~~ | If the applicant considers it necessary to revise the terms of the application or supporting documentation following review by the REC but before a final ethical opinion has been given, these may be included in the applicant's letter in response to the REC's request for further information or clarification (see Section 3). Changes to supporting documentation should be clearly highlighted, and the relevant documents given a new version number and date. At the discretion of the Chair, the revisions may then be reviewed in accordance with the procedures agreed for considering further information from the applicant. Where, exceptionally, a Notice of Substantial Amendment is submitted during the review process (see paragraph 6.11), it should be reviewed by the Chair/vice-Chair and at least one other member. | 1.74 | If the applicant considers it necessary to revise the terms of the application or supporting documentation following review by the REC but before a final ethical opinion has been given, these may be included in the applicant's letter in response to the REC's request for further information or clarification (see Section 3). For applications involving the NHS in England and Wales, this could include changes which have been requested by the Approvals Specialist in order to meet HRA assessment standards. Changes to supporting documentation should be clearly highlighted, and the relevant documents given a new version number and date. At the discretion of the Chair, the revisions may then be reviewed in accordance with the procedures agreed for considering further information from the applicant. Where, exceptionally, a Notice of Substantial Amendment is submitted during the review process (see paragraph 6.11), it should be reviewed by the Chair/vice-Chair and at least one other member. |
| **Section 2: Full meetings of a Research Ethics Committee** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| 2.38 | A REC may co-opt up to two additional members at any meeting of the REC for the purposes of that meeting. A person may be co-opted as a member only if they are a member of another REC within the UK Health Departments' Research Ethics Service or a member of MoDREC. Exceptionally, more than two members may be | 2.38 | A REC may co-opt up to two additional members at any meeting of the REC for the purposes of that meeting. A person may be co-opted as a member only if they are a member of another REC within the UK Health Departments' Research Ethics Service or a member of MoDREC. Exceptionally, more than two members (up to a |

| | | | |
|---|---|---|---|
| | co-opted with the agreement of the Head of Approvals Support provided that the meeting will not review any CTIMP applications. Deputy members may not act as co-opted members at their own REC, but may be co-opted by another REC. | | maximum of three) may be co-opted with the agreement of the Head of Approvals Support provided that the meeting will not review any CTIMP applications. Deputy members may not act as co-opted members at their own REC, but may be co-opted by another REC. |
| 2.39 | In exceptional circumstances, an officer of a REC may be co-opted to Chair a meeting of a different REC. The appropriate indemnity for this should be arranged ~~by the Member Support Manager.~~ | 2.39 | In exceptional circumstances, an officer of a REC may be co-opted to Chair a meeting of a different REC. The appropriate indemnity for this should be arranged where applicable. |
| 2.51 | The REC is required under the Clinical Trials Regulations to obtain advice before giving its opinion on an application relating to a CTIMP in which any subject of the trial is:<br>(a) a minor, i.e. a person under the age of 16 years.<br>(b) an adult incapable by reason of physical or mental incapacity to give informed consent to participation. | 2.51 | The REC is required under the Clinical Trials Regulations to obtain advice before giving its opinion on an application relating to a CTIMP in which any subject of the clinical trial is:<br>(a) a minor, i.e. a person under the age of 16 years.<br>(b) an adult incapable by reason of physical and mental incapacity to give informed consent to participation in the trial.<br>Note: Under the Clinical Trials Regulations consent endures any loss of capacity and therefore as long as the subject is capable of giving their informed consent to participate in the trial, the REC does not need to obtain expert advice. |

| | | | |
|---|---|---|---|
| 2.67 | External observers may be invited to attend REC meetings, subject to written invitation setting out the terms under which observer status is permitted, the signature of a confidentiality agreement, and the agreement of the REC at the meeting to be attended. Confidentiality agreements should be drawn up using the model in form SF2, which is in line with the duty of confidentiality accepted by REC members. SF2 is available on the HRA Hub and the signed copy should be uploaded to the meeting documents tab in HARP. | 2.67 | External observers may be invited to attend REC meetings, subject to written invitation setting out the terms under which observer status is permitted, the signature of a confidentiality agreement, and the agreement of the REC at the meeting to be attended. Confidentiality agreements should be drawn up using the model in form SF2, which is in line with the duty of confidentiality accepted by REC members. SF2 is available on the HRA Hub and the signed copy should be uploaded to the meeting documents tab in HARP. Observers may be sent a copy of the agenda but should not receive a copy of the applications to be reviewed at the meeting. |
| 2.68 | External observers should have no vested interest in any applications being considered at the meeting. R&D Directors and R&D managers should not generally be permitted to attend meetings of RECs at which applications for which they have research governance responsibilities are to be reviewed. However, where an NHS body is sponsoring the research, an R&D representative may attend the meeting for that item only alongside the Chief Investigator. In such cases, the R&D representative attends as the research sponsor, in accordance with paragraph 2.22 rather than as an observer. | 2.68 | External observers should have no vested interest in any applications being considered at the meeting. Where an observer does have a vested interest in an application being reviewed at the meeting, the observer should inform the REC of this. R&D Directors and R&D managers should not generally be permitted to attend meetings of RECs at which applications for which they have research governance responsibilities are to be reviewed. However, where an NHS body is sponsoring the research, an R&D representative may attend the meeting for that item only alongside the Chief Investigator. In such cases, the R&D representative attends as the research sponsor, in accordance with paragraph 2.22 rather than as an observer. |

| | | | |
|---|---|---|---|
| 2.72 | The Chair is responsible for the conduct of the business and for ensuring that the Committee reaches clearly agreed decisions on all matters. Where the Chair is unavailable, the meeting should normally be chaired by the vice-Chair or, if the vice-Chair is also unavailable, by the alternate vice-Chair. If all three officers are unavailable, ~~the appointing authority for the REC should be invited to appoint another member of the Committee or a co-opted member as a temporary vice-Chair. If it is not possible to arrange formal appointment prior to the meeting, or if a temporary vice-chair is appointed at the meeting itself, the appointing authority should be asked to ratify the appointment retrospectively.~~ | 2.72 | The Chair is responsible for the conduct of the business and for ensuring that the Committee reaches clearly agreed decisions on all matters. Where the Chair is unavailable, the meeting should normally be chaired by the vice-Chair or, if the vice-Chair is also unavailable, by the alternate vice-Chair. If all three officers are unavailable, an Officer of a different REC may be co-opted to chair the meeting in agreement with the Operational Manager, this applies to both full and Proportionate Review meetings. |
| 2.81 | The minutes should be submitted to the following meeting of the REC for ratification as a true record. Any necessary revisions should be incorporated in the final version of the minutes. If the revisions are minor, they may be made in manuscript on the face of the minutes and should be initialled and dated by the Approvals Officer/REC Manager. If not, a revised version of the minutes should be prepared. The final version should be signed and dated by the Chair and by the Approvals Officer/REC Manager or Approvals Administrator/REC Assistant. A PDF copy of the final signed version of the minutes must be uploaded to HARP. A copy of the initial draft minutes uploaded to HARP (watermarked 'management in confidence') should be replaced by the final version. Where revisions are made to the minutes, the Chair should consider the need to write to applicants correcting any inaccuracies or | 2.81 | The minutes should be submitted to the following meeting of the REC for ratification as a true record. Any necessary revisions should be incorporated in the final version of the minutes. If the revisions are minor, they may be made in manuscript on the face of the minutes and should be initialled and dated by the Approvals Officer/REC Manager. If not, a revised version of the minutes should be prepared. The final version should be signed and dated by the Chair and by the Approvals Officer/REC Manager or Approvals Administrator/REC Assistant. A PDF copy of the final signed version of the minutes must be uploaded to HARP. Electronically signed minutes are acceptable as long as the email from the chair attaching the signed minutes is also uploaded. A copy of the initial draft minutes uploaded to HARP (watermarked 'management in confidence') should be replaced by the final version. Where revisions |

| | | | |
|---|---|---|---|
| | clarifying points made in the letter sent after the meeting. However, no substantially new request for information may be made at this point. | | are made to the minutes, the Chair should consider the need to write to applicants correcting any inaccuracies or clarifying points made in the letter sent after the meeting. However, no substantially new request for information may be made at this point. |
| **Section 3: Giving an Ethical Opinion** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| ~~3.5~~ | ~~For all applications subject to a 60-day time limit, both CTIMPs and non-CTIMPs, the aim is for a final opinion to be given within 40 calendar days, allowing for the clock to stop once where a provisional opinion is given.~~ | | |
| 3.11 | Notification of the decision should be sent to the Chief Investigator (CI) within at least 10 working days of a full meeting (preferably fewer), or within 5 working days of a proportionate review by sub-committee. In the case of projects undertaken primarily for educational purposes, the decision letter or email and all further correspondence should be addressed to the student (or the first named student on the application if more than one is involved) and copied to the CI if different. All letters should be in the name of the Chair of the REC, it is acceptable for the letter to be signed by a vice-Chair or member of staff supporting the REC acting under delegated authority from the Chair. One of the following letters should be used:<br><br>Applications reviewed at a full meeting: | 3.11 | Notification of the decision should be sent to the Chief Investigator (CI) within at least 10 working days of a full meeting (preferably fewer), or within 5 working days of a proportionate review by sub-committee. In the case of projects undertaken primarily for educational purposes, the decision letter or email and all further correspondence should be addressed to the student (or the first named student on the application if more than one is involved) and copied to the CI if different. All letters should be in the name of the Chair of the REC, it is acceptable for the letter to be signed by a vice-Chair or member of staff supporting the REC acting under delegated authority from the Chair. One of the following letters <u>or email templates</u> should be used:<br><br>Applications reviewed at a full meeting: |

| | | | |
|---|---|---|---|
| | SL5 Favourable opinion<br>SL6 Unfavourable opinion<br>~~SL7~~ Provisional opinion with request for further information (this ~~may~~ be sent as a standalone email rather than as a letter).<br>SL8 Provisional opinion pending consultation with a referee.<br><br>Applications reviewed by sub-committee under proportionate review:<br>SL5 (PR) Favourable opinion<br>SL6 (PR) Unfavourable opinion<br>~~SL7~~ (PR) Provisional opinion with request for further information (this ~~may~~ be sent as a standalone email rather than as a letter).<br>SL8 (PR) No opinion – application referred to full meeting | | SL5 Favourable opinion<br>SL6 Unfavourable opinion<br>SL7 Provisional opinion with request for further information (this will usually be sent as a standalone email rather than as a letter).<br>SL8 Provisional opinion pending consultation with a referee.<br><br>Applications reviewed by sub-committee under proportionate review:<br>SL5 (PR) Favourable opinion<br>SL6 (PR) Unfavourable opinion<br>SL7 (PR) Provisional opinion with request for further information (this will usually be sent as a standalone email rather than as a letter).<br>SL8 (PR) No opinion – application referred to full meeting |
| 3.12 | The following information should in all cases be included in the letter or in enclosures:<br><br>~~• A summary of the ethical issues considered by the REC.~~<br>• A list of all documents reviewed at the meeting, giving correct version numbers and dates.<br>• A list of the members who were present for the discussion of the application or who submitted written comments on the application prior to the meeting. The list should indicate lay members and give the profession in the case of expert members.<br>• Declarations of interest by members, which were material to the application, and whether or not the member | 3.12 | The following information should in all cases be included in the letter or in enclosures:<br><br>• List of requests for further information from the applicant or additional conditions to be met, including an explanation of the reasons based on the RECs discussion.<br>• A list of all documents reviewed at the meeting, giving correct version numbers and dates<br>• A list of the members who were present for the discussion of the application or who submitted written comments on the application prior to the meeting. The list should indicate lay members and give the profession in the |

| | | | |
|---|---|---|---|
| | concerned took part in the review and voted on the decision (it is not necessary to give details of the interests, only that a declaration was made).<br>• The names of any observers present at the meeting.<br>• ~~A named contact point for receipt of queries from the applicant (the REC should agree which members will be available to support the Approvals Officer/REC Manager in handling queries).~~ | | case of expert members. This will be issued with the final opinion letter.<br>• Declarations of interest by members, which were material to the application, and whether or not the member concerned took part in the review and voted on the decision (it is not necessary to give details of the interests, only that a declaration was made). This will be included on the final opinion letter.<br>• The names of any observers present at the meeting. This will be confirmed on the final opinion letter. |
| ~~3.14~~ | ~~The summary of ethical issues should set out the main issues considered by the REC in deciding on its opinion. It is not necessary to include all the questions raised at the meeting, such as requests by lay members for explanation of technical points. However, it is important to record for future reference any ethical issues that the REC collectively discussed and resolved with the Chief Investigator at the meeting, and any clarifications given orally of the information contained in the application. It should not then be essential for the Chief Investigator to provide written confirmation on these points, unless the REC considers that further information, clarification or revision of the documentation is required after the meeting.~~ | | |
| 3.2~~1~~ | For clinical trials, as determined by the first 4 categories of ~~Q2 in~~ the IRAS ~~form~~, registration on a ~~publically~~ accessible database within 6 weeks ~~of the first participant being recruited is a standard condition~~. ~~For commercially~~ | 3.20 | For clinical trials, as determined by the first 4 categories of study in question 2 of the IRAS project filter page, it is a standard condition of the favourable opinion to register the research on a publicly accessible database within 6 weeks |

| | | | |
|---|---|---|---|
| | ~~sensitive research,~~ The applicant or sponsor can request a ~~to defer the requirement to register by contacting the Approvals Officer/REC Manager or~~ by emailing hra.studyregistration@nhs.net. | | of recruitment of the first participant. The applicant or sponsor can request a deferral of registration by emailing study.registration@hra.nhs.uk. The policy and procedure for the deferral process is published on the HRA website and provides more details. |
| 3.2~~2~~ | Examples of other conditions to be met prior to the start of the study (or the start at each site) might include:<br>• Specific additions or amendments to the participant information sheet or other study documentation.<br>• ~~Requirement for the Chief Investigator to undertake training in informed consent or GCP; where appropriate to the study.~~<br>• Requirement for the Chief Investigator to undertake training in informed consent or GCP; where appropriate to the study.<br>• Ensuring that investigators and other research staff have been trained to undertake interventions or procedures outside their routine competence.<br>• Reaching agreement with the responsible care organisation(s) on responsibilities for funding the plan for continuing care of participants at the end of the study.<br>• Ensuring data encryption is in place on the PCs or laptops to be used in the research.<br>• Obtaining or renewing a final certificate of insurance or indemnity to provide the cover specified in the REC application. (Note: Details of | 3.21 | Examples of other conditions to be met prior to the start of the study (or the start at each site) might include:<br>• Specific additions or amendments to the participant information sheet or other study documentation.<br>• Requirement for the Chief Investigator to undertake training in informed consent or GCP; where appropriate to the study.<br>• Ensuring that investigators and other research staff have been trained to undertake interventions or procedures outside their routine competence.<br>• Reaching agreement with the responsible care organisation(s) on responsibilities for funding the plan for continuing care of participants at the end of the study.<br>• Ensuring data encryption is in place on the PCs or laptops to be used in the research.<br>• Obtaining or renewing a final certificate of insurance or indemnity to provide the cover specified in the REC application. (Note: Details of the proposed cover must be provided in the application form as part of a valid application, but |

| | | | |
|---|---|---|---|
| | the proposed cover must be provided in the application form as part of a valid application, but issue or renewal of the final certificate may follow after the issue of a favourable opinion.)<br>• For Phase 1 studies in healthy volunteers, participants must be registered on 'The Over-Volunteering Prevention System' (TOPS). All relevant fields must be completed when the participant is registered, and the system should be updated as appropriate for each participant on an ongoing basis. | | issue or renewal of the final certificate may follow after the issue of a favourable opinion.)<br>• For Phase 1 studies in healthy volunteers, participants must be registered on 'The Over-Volunteering Prevention System' (TOPS). All relevant fields must be completed when the participant is registered, and the system should be updated as appropriate for each participant on an ongoing basis. |
| 3.2~~9~~ | Where the Committee or sub-committee requests further information from the applicant, it should decide in the initial review the procedures for considering that information and determining the REC's final opinion. These responsibilities should ~~normally~~ be delegated to one of the following:<br>(i) Designated REC supporting staff (eg. Approvals Officer/REC Manager).<br>(ii) Officer of the reviewing committee alone.<br>(iii) Officer of the reviewing committee and the designated lead reviewer for the study~~, and/or with support from REC supporting staff.~~<br>(iv) Chair or vice-chair, in oral or written consultation with one or more named members or deputy members that were present at the meeting or who submitted written comments on the application, or with a Scientific Officer.<br>(v) Exceptionally, a Sub-committee involving named members. | 3.2<u>8</u> | Where the Committee or sub-committee requests further information from the applicant, it should decide in the initial review the procedures for considering that information and determining the REC's final opinion. These responsibilities <u>should be</u> delegated to one of the following:<br>(i) Designated REC supporting staff (eg. Approvals Officer/REC Manager).<br>(ii) Officer of the reviewing committee alone.<br>(iii) Officer of the reviewing committee and the designated lead reviewer for the study.<br>(iv) Chair or vice-chair, in oral or written consultation with one or more named members or deputy members that were present at the meeting or who submitted written comments on the application, or with a Scientific Officer.<br>(v) Exceptionally, a Sub-committee involving named members. |

| | | | |
|---|---|---|---|
| 3.~~50~~ | An unfavourable opinion may be varied to a favourable opinion where the reasons for the opinion no longer apply. | 3.49 | An unfavourable opinion may be varied to a favourable opinion or to a provisional opinion where the reasons for the opinion no longer apply. |
| | | 3.57 | As per the requirements set out in GAfREC, for every application reviewed by a REC a research summary, including the REC decision, is published on the HRA website no earlier than 90 days after the date of the final opinion letter.<br>Sponsors may request a deferral of publication of some fields of the research summary by emailing study.registration@hra.nhs.uk. The policy and procedure for the deferral process is published on the HRA website and provides more details. |
| **Section 4: Proportionate Review** | | | |
| 4.12 | Where a sub-committee undertakes proportionate review of a new application, the quorum is three members with at least 6 months' service on a REC, including a Committee officer ~~(see also paragraph 7.10),~~ at least one expert member and at least one lay or lay plus member. | 4.12 | Where a sub-committee undertakes proportionate review of a new application, the quorum is three members with at least 6 months' service on a REC, including a Committee officer, at least one expert member and at least one lay or lay plus member.<br>If it is subsequently identified that a decision was issued by an inquorate PR Sub-Committee the matter should be referred to the Operational Manager. The Operational Manager will consider the application and decide whether the study should be re-reviewed at a quorate meeting. |
| **Section 5: Assessing the suitability of research sites** | | | |

| Para | SOP 7.4 | Para | SOP 7.5 |
|---|---|---|---|
| 5.11 | When there is a change of PI at a site in a CTIMP or Clinical Investigation of a Medical Device, ~~a Notice of Substantial Amendment should be submitted to the REC.~~ | 5.11 | When there is a change of PI at a non-NHS/HSC site in a CTIMP or Clinical Investigation of a Medical Device, a substantial amendment should be submitted. The applicant should submit a Substantial Amendment and also submit the non-NHS/HSC Site Assessment form and CV/evidence of professional registration for the PI. However, only questions 2 and 3 on the non-NHS/HSC Site Assessment Form need to be completed when the change relates to the appointment of a new PI. |
| ~~5.33~~ | ~~Where a site is not local to the REC and further information regarding the site is desired, contact should be made with a REC which is local to the site. This should be requested by contacting a REC which is local to the site.~~ | | |
| **Section 6: Amendments to research given a favourable opinion** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| 6.1 | 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 | 6.1 | 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 “non-substantial amendments”) do not need to be notified. ~~Where the amendment is substantial, the sponsor is required to submit a valid notice of amendment to the MHRA and/or 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.~~ | | started. Amendments that are not substantial (referred to in these SOPs as “non-substantial amendments”) do not need to be notified. |
| 6.2 | ~~An “amendment to a clinical trial authorisation” is defined broadly in the Clinical Trials Regulations as an amendment to any of the following:~~<br><br>~~(a) the terms of the request for clinical trial authorisation from the MHRA;~~<br>~~(b) the terms of the REC application;~~<br>~~(c) the protocol;~~<br>~~(d) any other particulars or documents submitted with the applications to the MHRA or the REC.~~ | 6.2 | Where the amendment is substantial, the sponsor is required to submit a valid amendment to the MHRA and/or 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. |
| 6.3 | ~~A “substantial amendment” is defined as an amendment that is likely to affect to a significant degree any of the following:~~<br><br>~~(a) the safety or physical or mental integrity of the subjects of the trial,~~<br><br>~~(b) the scientific value of the trial,~~ | 6.3 | An “amendment to a clinical trial authorisation” is defined broadly in the Clinical Trials Regulations as an amendment to any of the following:<br><br>(a) the terms of the request for clinical trial authorisation from the MHRA;<br>(b) the terms of the REC application;<br>(c) the protocol;<br>(d) any other particulars or documents submitted with the applications to the MHRA or the REC. |

| | | | |
|---|---|---|---|
| | ~~(c) the conduct or management of the trial, or~~<br><br>~~(d) the quality or safety of any investigational medicinal product used in the trial.~~ | | |
| 6.4 | ~~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.~~ | 6.4 | A "substantial amendment" is defined as an amendment that is likely to affect to a significant degree any of the following:<br>(a) the safety or physical or mental integrity of the subjects of the trial,<br><br>(b) the scientific value of the trial,<br><br>(c) the conduct or management of the trial, or<br><br>(d) the quality or safety of any investigational medicinal product used in the trial. |
| 6.5 | Where the sponsor requests an ethical opinion on a CTIMP, this should be given in all cases within 35 calendar days of receiving a valid notice of amendment; ~~although there should be an aim of giving an ethical opinion within 28 calendar days.~~ | 6.5 | Where the sponsor requests an ethical opinion on a CTIMP, this should be given in all cases within 35 calendar days of receiving a valid notice of amendment. |
| 6.12 | For CTIMPs, ~~the EU Notification of Substantial Amendment form should be used (also referred to as an Annex II Form) see paragraph 6.4). In accordance with the European Commission guidance, the form~~ may be submitted by any one of the sponsor, the sponsor's legal | 6.12 | For CTIMPs, the Substantial Amendment may be submitted by any one of the sponsor, the sponsor's legal representative, the Chief Investigator, or another person or organisation authorised by the sponsor. |

| | | | |
|---|---|---|---|
| | representative, the Chief Investigator, or another person or organisation authorised by the sponsor. | | |
| 6.19 | A ~~notice of~~ substantial amendment should be accepted as valid if all the following criteria are met:<br><br>(a)The ~~relevant notice of~~ amendment ~~form~~ has been completed in full, including the sponsor's amendment number. ~~For CTIMPs the notice of substantial amendment form should have been created in IRAS or via EudraCT. For non-CTIMPs, Research Tissue Banks and Research Databases, the notice of substantial amendment form should have been created in IRAS. The notice of substantial amendment form should be submitted by email for both CTIMPs and non-CTIMPs.~~<br><br>(b)Relevant extracts or new versions of revised documents have been submitted, showing the new version number and date and giving both the previous and new wording which is clearly identifiable.<br><br>(c) The ~~notice of~~ amendment has been authorised by the ~~named applicant on behalf of the sponsor (CTIMPs), or by the Chief Investigator and the sponsor's authorised representative (non-CTIMPs)~~[11]. For Research Tissue Bank applications, the ~~notice of~~ amendment should be electronically authorised by the applicant. For Research Database applications, the ~~notice of~~ amendment should be electronically authorised by the Data Controller. | 6.19 | A substantial amendment should be accepted as valid if all the following criteria are met:<br><br>(a)The amendment has been completed in full, including the sponsor's amendment number.<br><br>(b)Relevant extracts or new versions of revised documents have been submitted, showing the new version number and date and giving both the previous and new wording which is clearly identifiable.<br><br>(c) The ~~notice of~~ amendment has been <u>electronically</u> authorised by the <u>sponsor or authorised delegate</u>. For Research Tissue Bank applications, the amendment should be electronically authorised by the applicant. For Research Database applications, the amendment should be electronically authorised by the Data Controller.<br><br>(d) The study is still in progress, i.e. the end of the study has not yet been declared. 112<br><br>(e) In non CTIMPs, where the amendment proposes to include adults lacking capacity in the research for the first time, the additional documents listed in paragraph 13.53 should be submitted. This type of amendment should be reviewed by a full REC rather than by a sub-committee (see paragraph 13.55). |

| | | | |
|---|---|---|---|
| | (d) The study is still in progress, i.e. the end of the study has not yet been declared. 112<br><br>(e) In non CTIMPs, where the amendment proposes to include adults lacking capacity in the research for the first time, the additional documents listed in paragraph 13.53 should be submitted. This type of amendment should be reviewed by a full REC rather than by a sub-committee (see paragraph 13.55).<br><br>~~(f) Where the amendment seeks Section 34 approval under the Mental Capacity Act 2005, the additional documents listed in paragraph 13.32 should be submitted, and the study must have started prior to 1 October 2007 (see paragraph 13.13).~~<br><br>(g) Where the amendment proposes to change (including an increase or decrease) the exposure of participants to ionising radiation, or to include such exposure for the first time, Part B Section 3 of the ~~REC~~ application form in IRAS should be updated or completed (as appropriate). This should be submitted to the REC by a further electronic submission of the ~~REC~~ form.<br><br>(h) Where the amendment proposes to include existing or newly obtained tissue samples for the first time, Part B Section 5 of the ~~REC~~ application form in IRAS should be completed. This should be submitted to the REC by a further electronic submission of the REC form. | | (f) Where the amendment proposes to change (including an increase or decrease) the exposure of participants to ionising radiation, or to include such exposure for the first time, Part B Section 3 of the application form in IRAS should be updated or completed (as appropriate). This should be submitted to the REC by a further electronic submission of the form.<br><br>(g) Where the amendment proposes to include existing or newly obtained tissue samples for the first time, Part B Section 5 of the application form in IRAS should be completed. This should be submitted to the REC by a further electronic submission of the form. |

| | | | |
|---|---|---|---|
| 6.24 | ~~For CTIMPs, sponsors should be referred initially to the current guidelines from the European Commission in 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" (CT1, revision 3, March 2010) at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm. The sponsor may seek further advice at their discretion.~~ | 6.24 | In giving advice, 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. |
| 6.25 | ~~In giving advice, 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. | 6.25 | 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. |
| 6.26 | Guidance from RES is that the following changes should normally be regarded as substantial:<br>• Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value.<br>• Changes to the procedures undertaken by participants.<br>• Changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study. | 6.26 | Guidance from RES is that the following changes should normally be regarded as substantial:<br>• Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value.<br>• Changes to the procedures undertaken by participants.<br>• Changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study. |

| | | | |
|---|---|---|---|
| | • Significant 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.<br>114<br>• A change of sponsor(s) or sponsor's legal representative.<br>• Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a CI reference 6.81-6.83.<br>~~• In a CTIMP, addition of a new site and/or new PI not listed in the original application.~~<br>• A change to the insurance or indemnity arrangements for the study.<br>• A change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.<br>• Temporary halt of a study or temporary halt at a study site to protect participants from harm, and the planned restart of a study following a temporary halt (see paragraph 10.89-10.91).<br>• A change to the definition of the end of the study (see paragraph 10.94).<br>• Any other significant change to the protocol or the terms of the REC application. | | • Significant 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.<br>114<br>• A change of sponsor(s) or sponsor's legal representative.<br>• Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a CI reference 6.81-6.83.<br>• A change to the insurance or indemnity arrangements for the study.<br>• A change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.<br>• Temporary halt of a study or temporary halt at a study site to protect participants from harm, and the planned restart of a study following a temporary halt (see paragraph 10.89-10.91).<br>• A change to the definition of the end of the study (see paragraph 10.94).<br>• Any other significant change to the protocol or the terms of the REC application. |
| 6.27 | 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 amendments. | 6.27 | 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 amendments. |

| | | | |
|---|---|---|---|
| | Examples might be as follows:<br><br>• Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications.<br>• Changes to the Chief Investigator's research team.<br>• Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator in a CTIMP).<br>• Addition of any new NHS/HSC sites, or addition of any new non-NHS/HSC sites (except in CTIMPs and Clinical Investigations of Medical Devices -see paragraphs 6.72-6.73).<br>~~• Routine closure of sites at the end of the study.~~<br>• Changes in funding arrangements.<br>• Changes in the documentation used by the research team for recording study data.<br>• Changes in the logistical arrangements for storing or transporting samples within the duration of the project.<br>• Extension of the study beyond the period specified in the application form (see paragraph 10.9).<br>• Issue of an updated Investigator's Brochure or Summary of Product Characteristics relating to an investigational medicinal product<br>~~• Changes to the presentation of previously approved wording such as an approved advertisement being used in a different format.~~ | | Examples might be as follows:<br><br>• Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications.<br>• Changes to the Chief Investigator's research team.<br>• Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator in a CTIMP <u>at an NHS/HSC site</u>).<br>• Addition of any new NHS/HSC sites, or addition of any new non-NHS/HSC sites (except in CTIMPs and Clinical Investigations of Medical Devices -see paragraphs 6.72-6.73).<br>• Changes in funding arrangements.<br>• Changes in the documentation used by the research team for recording study data.<br>• Changes in the logistical arrangements for storing or transporting samples within the duration of the project.<br>• Extension of the study beyond the period specified in the application form (see paragraph 10.9).<br>• Issue of an updated Investigator's Brochure or Summary of Product Characteristics relating to an investigational medicinal product <u>(unless there is a change to the risk/benefit assessment for the trial).</u><br><br><u>This list of examples relates to non-substantial amendments for REC purposes. Applicants undertaking research in the NHS/HSC should also refer to IRAS help.</u> |

| | | | |
|---|---|---|---|
| 6.30 | 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 C, which has been agreed between RES and the MHRA and takes account of the guidance from the European Commission (see paragraph 6.24 above).~~ | 6.30 | It is the responsibility of the sponsor to decide whether a substantial amendment requires authorisation, or an ethical opinion, or both. |
| 6.4~~1~~ | In the case of CTIMPs, the 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~~. Where an unfavourable opinion on the amendment may be given on safety grounds, the Approvals Officer/REC Manager/Chair should correspond with the MHRA prior to the decision being taken (see the Memorandum of Understanding between RES and the MHRA). The MHRA is notified automatically of all opinions on substantial amendments and modified amendments through its access to HARP. Where the MHRA has been asked to authorise a substantial amendment, it will issue a written notice within 35 calendar days accepting the amendment or giving grounds for non-acceptance. It is the responsibility of the sponsor to arrange for the REC to be provided with a copy of the notice for information. | 6.4<u>0</u> | In the case of CTIMPs, the 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~~. Where an unfavourable opinion on the amendment may be given on safety grounds, the Approvals Officer/REC Manager/Chair should correspond with the MHRA prior to the decision being taken (see the Memorandum of Understanding between RES and the MHRA). The MHRA is notified automatically of all opinions on substantial amendments and modified amendments through its access to HARP. Where the MHRA has been asked to authorise a substantial amendment, it will issue a written notice within 35 calendar days accepting the amendment or giving grounds for non-acceptance. It is the responsibility of the sponsor to arrange for the REC to be provided with a copy of the notice for information. |
| ~~6.34~~ | ~~Non-substantial amendments do not require an ethical opinion.~~ | | |
| 6.3~~7~~ | ~~Except where paragraph 6.42 applies for amendments to add new NHS/HSC sites,~~ substantial amendments should be reviewed by a sub-committee of the REC (see Section | 6.3<u>6</u> | Substantial amendments should be reviewed by a sub-committee of the REC (see Section 7) or by the Committee itself. They may not be reviewed by the Chair acting alone, |

| | | | |
|---|---|---|---|
| | 7) or 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 6.48). ~~Substantial amendments for new NHS sites/PIs in CTIMP studies can be acknowledged, however they do not need to be reviewed by a sub-committee (see 6.67)~~. Applicants and sponsors may wish to submit ~~notices of~~ amendments ~~for~~ new NHS sites/PIs separately rather than as part of ~~another~~ notice of substantial amendment. | | except where the Chair has been given delegated authority at a meeting to review a modified amendment (see paragraph 6.48). Substantial amendments for new NHS sites/PIs in CTIMP studies can be acknowledged, however they do not need to be reviewed by a sub-committee (see 6.67). Applicants and sponsors may wish to submit amendments to add new NHS sites/PIs separately rather than as part of a Substantial Amendment notification. |
| | | 6.60 | By virtue of their design, studies which have been set up as Complex Innovative Trials (sometimes referred to as adaptive, platform or umbrella trials) may add different interventions or may recruit new categories of participants as the study progresses. For Complex Innovative Trials, it is acceptable for these changes to be submitted as a substantial amendment rather than as a new application. However, for trials to come under the heading of a Complex Innovative Trial, the protocol must have been approved by the REC on this basis when the study was originally reviewed and the methodology included in the protocol should have been clear about the scope for future phases, treatment arms or other adaptive features. Where the changes included in the amendment are particularly significant, the amendment may be reviewed by a Sub-Committee involving a larger number of members or by reviewing the amendment at a full REC meeting. |
| | | 6.64 | If an amendment to a study which did not previously require a REC review is submitted to the lead coordinating function, and the nature of the changes means that the |

| | | | |
|---|---|---|---|
| | | | project would now require a REC review under GAfREC (e.g. a study which previously only involved NHS staff was expanded to also recruit patients), the sponsor should be directed to seek advice from an Operational Manager in the lead nation for the study. |
| 6.6~~5~~ | Where the 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:<br><br>The favourable opinion should be issued to the applicant within 35 calendar days.<br>• The 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 condition 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.<br>• ~~Exceptionally, the main REC may also write directly to local RECs for non-NHS/HSC sites by letter or e-mail, explaining the specific concerns of the main REC~~ | 6.66 | Where the 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:<br><br>• The favourable opinion should be issued to the applicant within 35 calendar days.<br>• The 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 condition 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.<br>• In the light of any site-specific concerns, the REC may review the favourable opinion for a non-NHS site at any time (see paragraphs 10.101-10.122). |

| | | | |
|---|---|---|---|
| | ~~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 local RECs may be asked to review a particular aspect of the changes and to advise the REC by a specified date whether it has any concerns about the continued suitability of the site.~~<br>• ~~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.~~<br>• In the light of any site-specific concerns raised ~~by a local REC~~, the ~~main~~ REC may review the favourable opinion for a non-NHS site at any time (see paragraphs 10.101-10.122). | | |
| 6.6~~6~~ | The inclusion of a new ~~site, both NHS/HSC and~~ non-NHS/HSC site~~s~~, (not listed as a site in the original application), appointment of a new Principal Investigator or any other significant change to the management or conduct of the trial at a particular site is a substantial amendment, requiring notification to the REC on the European Commission Notice of Substantial Amendment Form. The REC should give an opinion within 35 calendar days of receipt of a valid notice of amendment. | 6.6<u>7</u> | The inclusion of a non-NHS/HSC site, (not listed as a site in the original application), appointment of a new Principal Investigator <u>at a non-NHS/HSC site</u>, or any other significant change to the management or conduct of the trial at a particular site is a substantial amendment, requiring notification to the REC on the European Commission Notice of Substantial Amendment Form. The REC should give an opinion within 35 calendar days of receipt of a valid notice of amendment. |
| 6.6~~7~~ | Where the amendment relates to the addition of a new NHS/HSC site, not listed on the original application form, ~~and/or PI, SL23B should be issued within 5 working days, confirming a favourable opinion on condition that~~ | 6.6<u>8</u> | Where the amendment relates to the addition of a new NHS/HSC site, not listed on the original application form, <u>there is no requirement to submit a substantial amendment to the REC. The site(s) are deemed to be approved within</u> |

| | | | |
|---|---|---|---|
| | ~~permission is given or continued by the R&D office(s) for the care organisation(s) involved. New sites should be manually added to the list of approved sites in HARP.~~ Responsibility for site assessment lies with the NHS care organisation. It is not necessary for the amendment to be reviewed or notified to the Committee. If any doubt arises whether the site(s) concerned are NHS/HSC sites, staff should seek clarification from the sponsor and/or the care organisation concerned. | | the terms of the favourable opinion for the study from the REC. Responsibility for site assessment lies with the NHS care organisation. It is not necessary for the amendment to be reviewed or notified to the Committee. If any doubt arises whether the site(s) concerned are NHS/HSC sites, staff should seek clarification from the sponsor and/or the care organisation concerned. |
| 6.6~~8~~ | If a substantial amendment is received which will require sub-committee review and it includes new sites as well as other changes, the amendment should be entered on HARP as a substantial amendment and reviewed by the sub-committee in the normal way. ~~If the amendment is then given a favourable opinion, the new site(s)/PI(s) should be added to HARP using the substantial amendment functionality for new sites/PIs. This will ensure there is a record on HARP of the new site(s)/PI(s). The site details should be manually added to the approval letter.~~ | 6.69 | If a substantial amendment is received which will require sub-committee review and it includes new sites as well as other changes, the amendment should be entered on HARP as a substantial amendment and reviewed by the sub-committee in the normal way. |
| 6.~~69~~ | Where the amendment includes any changes at non-NHS/HSC sites, the responsibility for site-assessment lies with the REC system. The non-NHS/HSC Site Assessment form should be submitted as part of the amendment and the amendment should be validated and reviewed by the REC. | 6.70 | Where the amendment includes any changes at non-NHS/HSC sites, the responsibility for site-assessment lies with the REC system. The non-NHS/HSC Site Assessment form should be submitted as part of the amendment and the amendment should be validated and reviewed by the REC. If the amendment is a change of PI at a non-NHS/HSC site review of the amendment may be delegated to an Operational Manager on behalf of the REC. |
| 6.7~~0~~ | The sponsor may extend the study to additional NHS/HSC sites, subject to obtaining permission from the NHS R&D | 6.71 | The sponsor may extend the study to additional NHS/HSC sites, subject to obtaining permission from the NHS R&D |

| | | | |
|---|---|---|---|
| | office prior to starting the research at the site. ~~Site-specific assessment is undertaken by the NHS R&D office as part of the research governance review.~~ There is no requirement for the REC to be notified of the new site. The site is deemed to be approved within the terms of the favourable opinion for the study from the REC. | | office prior to starting the research at the site. There is no requirement for the REC to be notified of the new site. The site is deemed to be approved within the terms of the favourable opinion for the study from the REC. |
| 6.7~~1~~ | Where the study is to be extended to a new non-NHS site, the NHS/HSC site assessment form should be submitted to the REC as part of a Notice of Substantial Amendment. | 6.72 | Where the study is to be extended to a new non-NHS site, the non-NHS/HSC site assessment form should be submitted to the REC as part of a Notice of Substantial Amendment. If the amendment is a change of PI at a non-NHS/HSC site review of the amendment may be delegated to an Operational Manager on behalf of the REC. |
| 6.7~~4~~ | The appointment of a new Principal Investigator at a site ~~(NHS/HSC sites and non-NHS/HSC sites)~~ in a CTIMP is a substantial amendment, requiring a favourable opinion from the REC. The procedures set out in paragraphs 6.66-6.71 should be followed. ~~Where possible, arrangements to notify the amendment and obtain a favourable opinion and permission from the host organisation should be made in advance by the sponsor so there is no interruption to the approvals in place. Where an interruption is unavoidable, for example due to an unforeseen absence, the sponsor should arrange for a suitable individual to act as interim PI and seek the necessary approvals as soon as possible. The trial may continue at the site pending confirmation of approval for the new PI. Protocol procedures may continue provided that the sponsor is satisfied that suitable interim arrangements are in place for supervising the study.~~ | 6.75 | In a CTIMP, the appointment of a new Principal Investigator at an NHS/HSC site is a non-substantial amendment. The appointment of a new Principal Investigator at new non-NHS/HSC site in a CTIMP is a substantial amendment, requiring a favourable opinion from the REC. The procedures set out in paragraphs 6.66-6.71 should be followed. |

| | | | |
|---|---|---|---|
| | | 6.76 | Where possible, arrangements to notify the amendment and obtain a favourable opinion and permission from the host organisation should be made in advance by the sponsor so there is no interruption to the approvals in place. Where an interruption is unavoidable, for example due to an unforeseen absence, the sponsor should arrange for a suitable individual to act as interim PI and seek the necessary approvals as soon as possible. The trial may continue at the site pending confirmation of approval for the new PI. Protocol procedures may continue provided that the sponsor is satisfied that suitable interim arrangements are in place for supervising the study. |
| **Section 7: Sub-committees** | | | |
| 7.9 | Deputy members ~~should not be appointed to serve on sub-committees in their own right~~**.** | 7.9 | Deputy members may participate in sub-committees in place of their "lead" member. |
| 7.13 | Sub-committee meetings may be conducted over the telephone. Where available, teleconferencing or video-conferencing facilities should be used. ~~If such facilities are not available, it is acceptable for business involving~~ | 7.13 | Sub-committee meetings may be conducted over the telephone. Where available, teleconferencing or video-conferencing facilities should be used. |

| | | | |
|---|---|---|---|
| | ~~the Chair and one other member only to be conducted over a normal telephone line.~~ | | |
| ~~7.25~~ | ~~The responsibilities of staff relation to sub-committee meetings are as follows:~~<br>~~(i) Preparing the agenda for meetings.~~<br>~~(ii) Distributing the agenda and papers at least 3 working days prior to a meeting.~~<br>~~(iii) Recording apologies for absence prior to meetings.~~<br>~~(iv) Recording attendance by members and referees at meetings.~~<br>~~(v) Advising meetings as necessary on compliance with standard operating procedures.~~<br>~~(vi) Making a written record of meetings.~~<br>~~(vii) Preparing the minutes of the meeting.~~<br>~~(viii) Issue the decision letter as appropriate~~. | | |
| 7.2~~6~~ | The responsibilities of the staff in relation to sub-committee business ~~conducted in correspondence~~ are:<br><br>(i) Distributing papers to members and specifying dates for written comments to be returned<br>(ii) Co-ordinating correspondence and arranging for written comments to be reviewed by the Chair if required.<br>(iii) Following up the decisions taken as appropriate.<br>(iv) Preparing minutes of the business (see paragraph 7.19).<br>(v) Destroying written comments from members once the minutes have been ratified (see paragraph 15.8). | 7.2<u>5</u> | The responsibilities of the staff in relation to sub-committee business are:<br><br>(i) Distributing papers to members and specifying dates for written comments to be returned<br><u>(ii) Recording attendance/participation by members and referees at meetings.</u><br><u>(iii) Co-ordinating correspondence and arranging for written comments to be reviewed by the Chair if required.</u><br><u>(iv) Advising meetings as necessary on compliance with standard operating procedures.</u><br><u>(v) Following up the decisions taken as appropriate.</u><br><u>(vi) Preparing minutes of the business (see paragraph 7.19).</u> |

| | | | |
|---|---|---|---|
| | (vi) Issue the decision letter as appropriate. | | (vii) Destroying written comments from members once the minutes have been ratified (see paragraph 15.8).<br>(viii) Issue the decision letter as appropriate. |
| **Section 8: Further review of research given a unfavourable opinion** | | | |
| SOP 7.4 | SOP 7.4 | Para | SOP 7.5 |
| 8.4 | The application should be ethically reviewed according to normal procedures. ~~In the case of studies requiring an assessment of site suitability for non-NHS/HSC sites, new applications for site assessment should be submitted and processed in the normal way.~~ | 8.4 | The application should be ethically reviewed according to normal procedures. |
| 8.5 | Where the application is being reviewed by a different REC, the Approvals Officer/REC Manager of the second REC can ~~contact the Approvals Officer/REC Manager of the original REC to request a copy of any correspondence relating to the previous review. This may include the unfavourable or provisional opinion letters if these have not been provided by the applicant.~~ All relevant correspondence should be included with the documentation submitted to members for review at the meeting. | 8.5 | Where the application is being reviewed by a different REC, the Approvals Officer/REC Manager of the second REC can obtain any of the original documents or correspondence relating to the previous review from HARP. All relevant correspondence should be included with the documentation submitted to members for review at the meeting. |
| 8.6 | It is highly desirable that the new application is re-booked with the original REC, as the members will already be familiar with the issues relating to the research and well placed to evaluate the changes made to the application. However, the applicant is entitled to apply to another appropriate REC if he/she prefers, except where the first REC is the only REC with the legal authority to review the | 8.6 | It is highly desirable that the new application is re-booked with the original REC, as the members will already be familiar with the issues relating to the research and well placed to evaluate the changes made to the application. However, the applicant is entitled to apply to another appropriate REC if he/she prefers, except where the first |

| | | | |
|---|---|---|---|
| | application (see paragraph 1.11). ~~The applicant can book directly with the REC if they would like to re-book to the same Committee or alternatively the applicant can contact CBS.~~ | | REC is the only REC with the legal authority to review the application (see paragraph 1.11). |
| 8.7 | ~~In the case of applications booked directly with a REC office or via the CBS, the Booking Operator should check that the original REC would be able to issue the final opinion within 60 days.~~ If there is a risk that the final opinion may not be issued by the original REC within 60 days, the resubmission should be booked for review by a different REC. Circumstances which may affect the final decision being issued by the original REC within 60 days may include the following:<br><br>The application is going to be received more than two weeks ahead of the REC's next closing date.<br>• The agenda for the next meeting of the REC is full.<br><br>• The next meeting of the REC will need to be cancelled due to a risk that it may not be attended by sufficient members. | 8.7 | If there is a risk that the final opinion may not be issued by the original REC within 60 days, the resubmission should be booked for review by a different REC. Circumstances which may affect the final decision being issued by the original REC within 60 days may include the following:<br><br>The application is going to be received more than two weeks ahead of the REC's next closing date.<br>• The agenda for the next meeting of the REC is full.<br><br>• The next meeting of the REC will need to be cancelled due to a risk that it may not be attended by sufficient members. |
| 8.22 | In rare circumstances, an applicant may dispute or be unable to comply with the additional conditions of a favourable opinion. The Medicines for Human Use (Clinical Trials Regulations) 2004 do not make provision to appeal decisions other than for an unfavourable opinion. However, it is RES policy that requests to appeal decisions other than unfavourable opinions will be considered. | 8.22 | In rare circumstances, an applicant may dispute or be unable to comply with the additional conditions of a favourable opinion. The Medicines for Human Use (Clinical Trials Regulations) 2004 do not make provision to appeal decisions other than for an unfavourable opinion. However, it is RES policy that requests to appeal decisions other than unfavourable opinions will be considered. |

| | | | |
|---|---|---|---|
| | Requests to appeal additional conditions of a favourable opinion should be brought to the attention of the Approvals Officer/REC Manager and discussed at a sub-committee of the REC which the applicant should be invited to attend in person or by teleconference to give further representation. If the REC agrees to amend the additional conditions, the favourable opinion letter should be reissued, correspondence uploaded, and a note added to HARP. If the REC does not agree to waive the additional condition(s) of the favourable opinion which are disputed, the procedures set out in paragraph 8.16 should be followed. The applicant can either comply with the conditions or the opinion could be varied ~~to an unfavourable opinion which means that the full application could then be resubmitted as a new application or the applicant may request to appeal the unfavourable opinion.~~ This process may only be undertaken once for a study. | | Requests to appeal additional conditions of a favourable opinion should be brought to the attention of the Approvals Officer/REC Manager and discussed at a sub-committee of the REC which the applicant should be invited to attend in person or by teleconference to give further representation. If the REC agrees to amend the additional conditions, the favourable opinion letter should be reissued, correspondence uploaded, and a note added to HARP. If the REC does not agree to waive the additional condition(s) of the favourable opinion which are disputed, the procedures set out in paragraph 8.16 should be followed. The applicant can either comply with the conditions or the opinion could be varied. This process may only be undertaken once for a study. |
| **Section 10: Monitoring of research given a favourable opinion** | | | |
| SOP 7.4 | SOP 7.4 | Para | SOP 7.5 |
| 10.2 | The general policy from RES is that the REC should keep under review the favourable ethical opinion given to any research study in the light of regular progress reports and significant developments in the research. This applies equally to CTIMPs and to other types of research, except | 10.2 | The general policy from RES is that the REC should keep under review the favourable ethical opinion given to any research study in the light of regular progress reports <u>(where required)</u> and significant developments in the research. This applies equally to CTIMPs and to other |

| | | | |
|---|---|---|---|
| | in relation to safety reporting where different provisions apply. | | types of research, except in relation to safety reporting where different provisions apply. |
| 10.9 | The favourable ethical opinion of the REC for a specific research study applies for the duration of the study, except where action is taken to suspend or terminate the opinion (see paragraphs 10.102ff). 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 sub-studies, or extension of follow-up. Where the duration of the study is to be extended beyond the period specified in the application form, ~~there is no need to notify or seek approval from the REC.~~ ~~However,~~ annual progress reports should continue to be submitted if the study duration is extended in this way, giving reasons for the extra time needed to complete the research – see paragraphs 10.12-10.18. | 10.9 | The favourable ethical opinion of the REC for a specific research study applies for the duration of the study, except where action is taken to suspend or terminate the opinion (see paragraphs 10.102ff). 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 sub-studies, or extension of follow-up. Where the duration of the study is to be extended beyond the period specified in the application form, <u>the REC should be notified.</u> Annual progress reports should continue to be submitted if the study duration is extended in this way, giving reasons for the extra time needed to complete the research – see paragraphs 10.12-10.18. |
| 10.10 | ~~It should be noted that continuation of the ethical opinion only applies to the study as described in the application, the protocol and any amendments made by the sponsor. Further applications should be made for ethical approval where required to undertake additional studies. In the case of studies involving human tissue which is 'relevant material' under the Human Tissue Act 2004, samples held in England, Wales and Northern Ireland, may be retained after the declaration of the end of the trial, for analysis or verification of research data for up to one year. After this period legal authority to hold any human tissue under the ethical approval for this project will expire.~~ | 10.10 | <u>In England, Wales and Northern Ireland, samples may be held without a HTA license after the end of study date has been reached, for verification or quality checking of the research data. This should be detailed in the protocol which is approved by the REC and should be for no longer than 12 months. After this period legal authority to hold any human tissue under the ethical approval for this project will expire. To ensure that any continued storage is lawful, either the tissue must be held on premises with a storage licence from the Human Tissue Authority, or an application made for ethical review of another project before the favourable ethical opinion (including the additional time after the declaration of the end of study, if applicable) of</u> |

| | | | |
|---|---|---|---|
| | | | the existing project expires. Otherwise the tissue would need to be destroyed in accordance with the HTA Codes of Practice. If additional time is needed to undertake the main analysis, then the REC should be informed of this before the end of study is declared. |
| 10.11 | Progress reports on ~~all research with a favourable opinion~~ should be submitted to the REC at least annually. The due date for receipt of the report is 30 days following the anniversary of the date on which the favourable opinion was given. Reports should continue to be submitted at least annually until the end of the study is notified, except where paragraph 10.18 applies. The REC may request that more regular reports should be submitted or may request an additional progress report at any time. | 10.11 | For studies with a favourable opinion, progress reports on all research with a favourable opinion should be submitted to the REC at least annually if they were reviewed at a full REC meeting and have an expected duration of more than two years. Progress reports should also be submitted on an annual basis for Research Tissue Banks and Research Databases to the REC. There is no requirement to submit a progress report for Proportionate Review studies or for studies also where the duration of the study is two years or less. Where required, the due date for receipt of the report is 30 days following the anniversary of the date on which the favourable opinion was given. Reports should continue to be submitted at least annually until the end of the study is notified, except where paragraph 10.17 applies. The REC may request that more regular reports should be submitted or may request an additional progress report at any time. |
| 10.13 | Progress reports should be acknowledged (SL37 may be used) and reviewed by the Committee (or reviewed by a member of staff on behalf of the Committee). The Committee should be notified of the receipt of the report (see paragraph 2.13). Copies or summaries may be distributed to members. | 10.13 | Progress reports should be acknowledged (SL37 may be used) and reviewed by the Committee (or reviewed by a member of staff on behalf of the Committee). When reviewing annual progress reports, staff should escalate any concerns about the study to the Chair or operational manager. The Committee should be notified of the receipt |

| | | | |
|---|---|---|---|
| | | | of the report (see paragraph 2.13). Copies or summaries may be distributed to members. |
| 10.16 | Where a progress report is not received by the due date, staff should send the reminder SL38. If the report is still not received after a further period of one month, consideration should be taken in terms of what further action should be taken. Further guidance on review of a favourable opinion, including possible suspension or termination, is at paragraphs 10.101. | 10.16 | Where a progress report is required and is not received by the due date, staff should send the reminder SL38. If the report is still not received after a further period of one month, consideration should be taken in terms of what further action should be taken. Further guidance on review of a favourable opinion, including possible suspension or termination, is at paragraphs 10.101. |
| ~~10.31~~ | ~~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, these may be confidentially destroyed and there is no requirement to acknowledge receipt.~~ | 10.30 | If a Serious Adverse Event has occurred in a CTIMP but the SAE is not related to the Investigational Medicinal Product(s) (IMP), this would not meet the definition of a SUSAR and does not need to be reported to the MHRA or HRA as a SUSAR. It would be expected that where the event is related to a licensed non-investigational medicinal product (NIMP), the manufacturer of the non-IMP is informed of any significant safety findings and use of the yellow card scheme is encouraged. If there is any question that the unexpected SAE could be due to the IMP then it should be reported to the MHRA and the REC as a SUSAR for the IMP. All events should be recorded in the Case Report Form/study documentation regardless as to whether they were related to an IMP or to the non-IMP treatment. |
| 10.3~~3~~ | ~~The European Commission guidance notes that other~~ events may occur during a clinical trial that may be relevant to participant safety and require action to protect | 10.32 | Events may occur during a clinical trial that may be relevant to participant safety and require action to protect |

| | | | |
|---|---|---|---|
| | participants but do not meet the definition of a SUSAR. These include:<br>(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,<br><br>(b) 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:<br><br>- 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),<br><br>- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,<br><br>- a major safety finding from a newly completed animal study (such as carcinogenicity),<br><br>- 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.<br><br>(c) the conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects. | | participants but do not meet the definition of a SUSAR. These include:<br>(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,<br><br>(b) 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:<br><br>- 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),<br><br>- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,<br><br>- a major safety finding from a newly completed animal study (such as carcinogenicity),<br><br>- 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.<br><br>(c) the conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects. |

| | | | |
|---|---|---|---|
| 10.3~~4~~ | These events/observations are not to be reported as SUSARs but might require other action such as urgent safety measures, substantial amendments or early termination of a trial. Where such actions are not taken ~~the European Commission guidance recommends~~ that the sponsor informs competent authorities and ethics committees of any safety issues which might materially alter the current risk/benefit assessment of the IMP. | 10.33 | These events/observations are not to be reported as SUSARs but might require other action such as urgent safety measures, substantial amendments or early termination of a trial. Where such actions are not taken it is recommended that the sponsor informs competent authorities and ethics committees of any safety issues which might materially alter the current risk/benefit assessment of the IMP. |
| 10.3~~5~~ | In the case of double-blinded trials, ~~the European Commission guidance recommends~~ that the sponsor should normally report SUSARs, after unblinding, to competent authorities, ethics committees and EVCTM (any waivers of the requirement for unblinded reporting should be agreed with the MHRA).. Unblinded information should only be accessible to those who need to be involved in safety reporting or who are involved in ongoing safety evaluation during the trial. The blind should be maintained for persons responsible for the ongoing conduct of the study (e.g. study management, monitors, investigators) or for analysis and interpretation of results. Investigators should only receive unblinded information if necessary for safety reasons. | 10.34 | In the case of double-blinded trials, it is recommended that the sponsor should normally report SUSARs, after unblinding, to competent authorities, ethics committees and EVCTM (any waivers of the requirement for unblinded reporting should be agreed with the MHRA).. Unblinded information should only be accessible to those who need to be involved in safety reporting or who are involved in ongoing safety evaluation during the trial. The blind should be maintained for persons responsible for the ongoing conduct of the study (e.g. study management, monitors, investigators) or for analysis and interpretation of results. Investigators should only receive unblinded information if necessary for safety reasons. |
| ~~10.40~~ | ~~The recommended format and content of the ASR (as set out in the ICH E2F guideline) is summarised at Annex F. It should include an Executive Summary which provides a concise summary of the important information in the report and is suitable for review by REC members as a stand-alone document.~~ | | |

| | | | |
|---|---|---|---|
| 10.~~41~~ | ASRs should include or 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. SSARs related to active comparators or placebo used in relevant trials should be included (there is no need for a separate ASR for comparators). | 10.39 | ASRs should include or 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 worldwide, as well as those in the UK. SSARs related to active comparators or placebo used in relevant trials should be included (there is no need for a separate ASR for comparators). |
| ~~10.45~~ | ~~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).~~ | | |
| 10.~~54~~ | 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 European Commission guidance~~ to establish an independent Data Monitoring Committee (DMC) to advise on safety issues. (Guidance for RECs on DMCs is available on the HRA website.) 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. | 10.51 | 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 to establish an independent Data Monitoring Committee (DMC) to advise on safety issues. (Guidance for RECs on DMCs is available on the HRA website.) 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. |
| 10.~~55~~ | Sponsors are required to submit complete data on all SUSARs ~~occurring in EU member states to EVCTM. This~~ | 10.52 | Sponsors are required to submit complete data on all SUSARs, in accordance with published by the MHRA. In |

| | | | |
|---|---|---|---|
| | ~~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 REC so that any implications for the ethics of the trial can be considered in parallel. | | the UK regulatory context, the MHRA will actively monitor the safety of clinical trials. Where the MHRA raises safety concerns with the sponsor, it will directly inform the REC so that any implications for the ethics of the trial can be considered in parallel. |
| 10.56 | Annual 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 Executive Summary. The REC is not required to make a detailed assessment of the report as a whole or the line listings.<br><br>The purpose of the review is to:<br>• Check the accuracy of the risk/benefit analysis as described in the participant information sheet.<br>• Consider the possible need for new information to be given to participants and their consent sought to continue in the study.<br>• Consider any other issue that may be relevant to the ethics of the trial. | 10.56 | Annual safety reports <u>can be acknowledged by a member of staff on behalf of the REC</u> <u>and may also</u> be reviewed by the Chair and/<u>or pharmacist.</u> The review may take place in correspondence or at a sub-committee or Committee meeting. The review may be confined to the Executive Summary. The REC is not required to make a detailed assessment of the report as a whole or the line listings.<br><br>The purpose of the review is to:<br>• Check the accuracy of the risk/benefit analysis as described in the participant information sheet.<br>• Consider the possible need for new information to be given to participants and their consent sought to continue in the study.<br>Consider any other issue that may be relevant to the ethics of the trial. |
| 10.92 | The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the REC in writing that a | 10.9<u>0</u> | The Clinical Trials Regulations provide that the sponsor should notify the MHRA and the REC in writing that a |

| | | | |
|---|---|---|---|
| | CTIMP has ended within 90 days of the conclusion of the trial. In the case of an international trial, ~~guidance from the European Commission is that~~ the sponsor is only required to notify the conclusion of the trial as a whole. Where the UK arm of a trial ends in advance of the conclusion in ~~all Member States,~~ this may be notified voluntarily (the form for declaring the end of the trial ~~should not~~ be used in this case). | | CTIMP has ended within 90 days of the conclusion of the trial. In the case of an international trial the sponsor is only required to notify the conclusion of the trial as a whole. Where the UK arm of a trial ends in advance of the conclusion in other countries, this may be notified voluntarily (the form for declaring the end of the trial can be used in this case). |
| 10.9~~5~~ | 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). ~~A Notice of~~ Substantial Amendment could be submitted alongside a declaration of early termination where it is necessary to seek ethical review of related actions such as informing participants and arranging continuing care and follow-up outside the trial. | 10.92 | Declarations of the conclusion or early termination of a CTIMP should be in the form available on the MHRA website. A substantial amendment may need to be submitted alongside a declaration of early termination where it is necessary to seek ethical review of related actions such as informing participants and arranging continuing care and follow-up outside the trial. |
| ~~10.103~~ | Written representations regarding such concerns should be sent to the Director of the Approvals Service. The Director of the Approvals Service or delegated staff will acknowledge receipt of a written concern regarding a REC opinion within 3 working days. | 10.102 | Written representations regarding such concerns should be sent to the Head of Corporate Governance & Risk and Director of the Approvals Service. The Director of the Approvals Service or delegated staff will acknowledge receipt of a written concern regarding a REC opinion within 3 working days. Where the concern is related to a REC based in the Devolved Administrations, the notification will be forwarded on for investigation by the equivalent postholders in Scotland, Wales or Northern Ireland. |

| | | | |
|---|---|---|---|
| 10.10~~4~~ | The Director of Approvals Service will consider the concern seeking further information from the correspondent and/or advice from others as necessary to determine whether it meets the criteria in para 10.103 and may be accepted or may be closed. This process should be undertaken within ~~14~~ calendar days. | 10.103 | The Head of Corporate Governance & Risk and Director of Approvals Service will consider the concern seeking further information from the correspondent and/or advice from others as necessary to determine whether it meets the criteria in para 10.101 and may be accepted or may be closed. This process should be undertaken within 10 working days. |
| 10.10~~5~~ | Where it is considered that the concern is related to the criteria in paragraph 10.10~~3~~ and presents relevant new information not originally considered by the REC, then the Director of Approvals Service ~~or delegated staff will~~ conduct an initial review of the REC decision, seeking advice from others as necessary, to determine:<br>• compliance of REC review with applicable SOPs;<br>• whether the REC had clearly and appropriately addressed the information presented in the concern/challenge at the time of their review;<br>• whether the protocol had been subject to appropriate scientific critique (“peer review”). | 10.104 | Where it is considered that the concern is related to the criteria in paragraph 10.101 and presents relevant new information not originally considered by the REC, then the Director of Approvals Service will appoint a Complaints Lead to conduct an initial review of the REC decision, seeking advice from others as necessary, to determine:<br>• compliance of REC review with applicable SOPs;<br>• whether the REC had clearly and appropriately addressed the information presented in the concern/challenge at the time of their review;<br>• whether the protocol had been subject to appropriate scientific critique (“peer review”).<br>• whether the nature of the concern or issue raised could attract media or other attention |
| 10.10~~6~~ | Where the concern does not relate to the categories set out in paragraph 10.10~~3~~ or is deemed not to present relevant new information it may still be taken forward for determination of compliance with SOPs and/or REC review | 10.105 | Where the concern does not relate to the categories set out in paragraph 10.101 or is deemed not to present relevant new information it may still be taken forward for determination of compliance with SOPs and/or REC review |

| | | | |
|---|---|---|---|
| | of the opinion at the discretion of the Director of Approvals Service, taking advice from others as necessary. | | of the opinion at the discretion of the Director of Approvals Service, taking advice from others as necessary. |
| 10.10~~7~~ | Depending on the outcome of the initial review of the REC opinion the Director of Approvals Service may either:<br>• close the matter and issue a formal response, where the REC review was fully compliant with SOPs and appropriately and fully addressed the concern;<br>• liaise with the REC Chair to respond to the concerns raised;<br>• require the REC to review its opinion in the light of the new information presented. | 10.106 | Depending on the outcome of the initial review of the REC opinion the Complaints Lead in liaison with the Director of Approvals Service may either:<br>• close the matter and issue a formal response, where the REC review was fully compliant with SOPs and appropriately and fully addressed the concern;<br>• liaise with the REC Chair to respond to the concerns raised;<br>• require the REC to review its opinion in the light of the new information presented. |
| 10.10~~8~~ | Where it is decided that the REC should review its opinion based on the new information presented, the study should normally be allocated to the next full meeting of the REC. A senior member of the Operations team should also attend the meeting. Depending upon timing it may be necessary to convene an ~~extra-ordinary~~ meeting of the REC. | 10.107 | Where it is decided that the REC should review its opinion based on the new information presented, the study should normally be allocated to the next full meeting of the REC. A senior member of the Operations team and/or the Complaints Lead should also attend the meeting. Depending upon timing it may be necessary to convene an additional meeting of the REC. |
| 10.10~~9~~ | Where the REC is required to review its opinion the ~~Director of Approvals Service, or delegated staff,~~ shall inform the person raising the concern of this and the associated timescale for re-review. | 10.108 | Where the REC is required to review its opinion the Complaints Lead, shall inform the person raising the concern of this and the associated timescale for re-review. The Head of Corporate Governance & Risk will issue the formal acknowledgement to the complainant and will also |

| | | | |
|---|---|---|---|
| | | | keep the complainant informed of any extensions to the timeline for review. |
| 10.1~~10~~ | Where, following the formal notification of the outcome of the initial review and/or subsequent REC review of the concern to the individual or body raising the concern continues to formally challenge the REC opinion (or revised opinion following REC review); then such further formal challenges should, where they have not been sent directly, be forwarded to the appointing authority lead for consideration. | 10.109 | The Complaints Lead should submit the outcome of the REC review to the Head of Corporate Governance & Risk and Director of the Approvals Service. The formal response to the individual who raised the concern will be issued by the Head of Corporate Governance & Risk. The Complaints Lead may also need to issue a separate communication from the REC to the Chief Investigator and Sponsor in order to notify them of the outcome and any further follow up required. |
| ~~10.141~~ | ~~If the final report is not received within one year of the conclusion of the research, a reminder letter should be sent (SL41 may be used).~~ | | |
| **Section 12: Research involving human tissue** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| 12.2 | Under the Human Tissue (Scotland) Act 2006, the statutory provisions relating to research apply only to research involving tissue and organs from the deceased. A summary of these provisions is at Annex H. The Scottish Government has ~~issued separate guidance on how the principles of the HT Act apply to Scottish research generally~~. However, where a Scottish REC is considering an application for research involving human tissue from | 12.2 | Under the Human Tissue (Scotland) Act 2006, the statutory provisions relating to research apply only to research involving tissue and organs from the deceased. A summary of these provisions is at Annex H. The Scottish Government has established an independent non-statutory accreditation scheme that applies standards for the collection and provision of tissue and organs from NHS patients by Scottish Health Boards for use in research. |

| | | | |
|---|---|---|---|
| | England, Wales or Northern Ireland, the full procedures set out in this section will apply. | | Accreditation is required for facilities (hereafter termed NHS Scotland biorepositories) working within Scottish Health Boards that are collecting and storing tissues from NHS Scotland patients and are providing access to retained tissue for future research. NHS Scotland biorepositories can also provide oversight of local research tissue banks to ensure that accreditation standards are applied. Accreditation is not required when a Scottish Health Board is only involved in the collection and storage of tissues for use in specific NHS REC approved projects and when the surplus tissue is subsequently destroyed in an appropriate manner or transferred to an accredited NHS Scotland biorepository following completion of the project. Accreditation is subject to a positive opinion on the activities given by a Scottish REC. However, where a Scottish REC is considering an application for research involving human tissue from England, Wales or Northern Ireland, the full procedures set out in this section will apply. |
| 12.4 | Analysing human DNA in material ~~from the body of a living person~~ (or using the results of DNA analysis) without consent, in circumstances where they are unable to identify the tissue donor and not likely to be able to do so in future (see paragraphs 16-18 of Annex H). | 12.4 | Analysing human DNA in cellular material (or using the results of DNA analysis) without consent, in circumstances where they are unable to identify the tissue donor and not likely to be able to do so in future (see paragraphs 16-18 of Annex H). |
| 12.8 | Under the Human Tissue (Scotland) Act 2006, research must be approved in writing where it takes place on an organ retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal. Approval is | 12.8 | Under the Human Tissue (Scotland) Act 2006, research must be approved in writing where it takes place on an organ retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal. Approval is |

| | | | |
|---|---|---|---|
| | also required for new research on organs retained from a post-mortem examination that took place before 1 September 2006. An Order made by Scottish Ministers under the Act specifies that such approvals must be given by:<br><br>• Any ethics committee established or recognised under the Medicines for Human Use (Clinical Trials) Regulations 2004, or;<br><br>• Any other committee established to advise on the ethics of research investigations in human beings and recognised for that purpose by or on behalf of the Secretary of State or the Scottish Ministers. This includes all RECs established under GAfREC. | | also required for new research on organs retained from a post-mortem examination that took place before 1 September 2006. An Order made by Scottish Ministers under the Act specifies that such approvals must be given by:<br><br>• Any ethics committee established or recognised under the Medicines for Human Use (Clinical Trials) Regulations 2004, or;<br><br>• Any other committee established to advise on the ethics of research investigations in human beings and recognised for that purpose by or on behalf of the Secretary of State or the Scottish Ministers. This includes all RECs established under GAfREC. However, operationally, it would be beneficial for an application to be considered by a Scottish REC with knowledge of the requirements of Scottish accreditation scheme (section 12.2). |
| 12.9 | The Human Tissue (Scotland) Act 2006 does not require ethical approval where the research involves tissue blocks and slides retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal, or tissues and organs retained from a hospital post-mortem examination, and there is authorisation for its use in research. However, under guidance issued on the Act in Scotland those responsible for the research project would be expected to obtain REC approval | 12.9 | The Human Tissue (Scotland) Act 2006 does not require ethical approval where the research involves tissue blocks and slides retained from a post-mortem examination carried out on the instructions of the Procurator Fiscal, or tissues and organs retained from a hospital post-mortem examination, and there is authorisation for its use in research. However, under guidance issued on the Act in Scotland those responsible for the research project would be expected to obtain REC approval. In addition to this, the |

| | | | |
|---|---|---|---|
| | | | General Policy set out in section 12.3 also applies in Scotland with respect to tissue from the living. |
| 12.11 | In some cases, consent to the storage and use of tissue in research is not legally required by the HT Act, in particular for existing holdings and, subject to ethical approval, tissue from living persons not identifiable to the researcher. However, this does not mean that all such tissue should be used freely and without regard to issues of consent or other ethical considerations. The Human Tissue Authority (HTA) Code of Practice on Consent gives advice on questions to be considered in relation to the use of existing holdings in research. RECs should take compliance with this advice into account in a proportionate way in discussion with applicants. | 12.11 | In some cases, consent to the storage and use of tissue in research is not legally required by the HT Act, in particular for existing holdings and, subject to ethical approval, tissue from living persons not identifiable to the researcher. However, this does not mean that all such tissue should be used freely and without regard to issues of consent or other ethical considerations. The Human Tissue Authority (HTA) Code of Practice on Consent gives advice on questions to be considered in relation to the use of existing holdings in research. RECs should take compliance with this advice into account in a proportionate way in discussion with applicants. Similarly for tissue collections in Scotland, RECs should take into account the requirements of the accreditation scheme for NHS Scotland biorepositories (section 12.2). |
| 12.12 (ii) | Application for approval of a research tissue bank (RTB), which may confer generic ethical approval prospectively for a range of research to be carried out by the establishment responsible for the bank and/or by other researchers to whom tissue is released by the bank within the conditions of the ethical approval (see paragraphs 12.21-12.35). Such approval may be given for a period of up to 5 years and will be renewable. A storage licence will be required from the HTA for banks storing relevant material in England, Wales or Northern Ireland. | 12.12 (ii) | Application for approval of a research tissue bank (RTB), which may confer generic ethical approval prospectively for a range of research to be carried out by the establishment responsible for the bank and/or by other researchers to whom tissue is released by the bank within the conditions of the ethical approval (see paragraphs 12.21-12.35). Such approval may be given for a period of up to 5 years and will be renewable. A storage licence will be required from the HTA for banks storing relevant material in England, Wales or Northern Ireland. In Scotland, NHS Scotland biorepositories need to be accredited through the |

| | | | |
|---|---|---|---|
| | | | independent accreditation scheme established by the Scottish Government (see paragraph 12.2). |
| 12.15 | Project-based applications should be made using the normal REC application form and in accordance with normal booking procedures (see section 1). The application should be allocated as follows:<br>• CTIMPs should be allocated to recognised committees in accordance with normal procedures (see section 1).<br>• Non-CTIMPs seeking ethical approval for the purposes of the HT Act should normally be allocated for review by a REC in England, Wales or Northern Ireland. However, they could be reviewed by a recognised REC in Scotland and this might be appropriate where for example the research is being conducted in (or involves tissue from) both Scotland and another part of the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to Scotland A REC.<br>• Other non-CTIMPs taking place anywhere in the UK and submitted for ethical review under departmental policy or on a voluntary basis, but not seeking ethical approval for the purposes of the HT Act, may generally be allocated to any REC in the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to the designated REC in Scotland.<br>• In Scotland, non-CTIMPs seeking ethical approval for the purposes of the Human Tissue (Scotland) Act 2004 and associated guidance should normally be allocated | 12.15 | Project-based applications should be made using the normal REC application form and in accordance with normal booking procedures (see section 1). The application should be allocated as follows:<br>• CTIMPs should be allocated to recognised committees in accordance with normal procedures (see section 1).<br>• Non-CTIMPs seeking ethical approval for the purposes of the HT Act should normally be allocated for review by a REC in England, Wales or Northern Ireland. However, they could be reviewed by a recognised REC in Scotland and this might be appropriate where for example the research is being conducted in (or involves tissue from) both Scotland and another part of the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to Scotland A REC.<br>• Other non-CTIMPs taking place anywhere in the UK and submitted for ethical review under departmental policy or on a voluntary basis, but not seeking ethical approval for the purposes of the HT Act, may generally be allocated to any REC in the UK. Where any of the participants are adults with incapacity in Scotland, the application should be made to the designated REC in Scotland (Scotland A REC).<br>• In Scotland, non-CTIMPs seeking ethical approval for the purposes of the Human Tissue (Scotland) Act 2004 and associated guidance should normally be allocated |

| | | | |
|---|---|---|---|
| | to a Scottish REC but may be allocated to a REC in England if necessary (see paragraph 12.8). | | to a Scottish REC but may be allocated to a REC in England if necessary (see paragraph 12.8). |
| 12.19 | • The researcher may ~~hold on to~~ the tissue without a licence under the original REC approval provided it is being held as a record of the completed research project, for example, to verify research data. ~~Storage for this purpose without a licence should continue for no longer than necessary.~~ If the tissue continues to be stored without a licence for the purpose of any other research project, further ethical approval should be sought using either the project-specific or RTB application process. | 12.19 | • The researcher may retain the tissue without a HTA licence under the original REC favourable opinion provided it is being held as a record of the completed research project, for example, to verify and quality check the research data. If additional time is needed to undertake the main analysis, then the REC should be informed of this before the end of study is declared. Storage without a licence for verification and quality checking should be for no longer than 12 months after the end of study has been reached and should be in accordance with the length of time set out in the protocol. If the tissue continues to be stored without a licence for the purpose of any other research project, a further ethical opinion should be sought before the favourable ethical opinion (including the additional time after the declaration of the end of study, if applicable) for the existing project expires.<br>• Where a researcher in Scotland makes a specific project-based application but also plans to store tissue collected from NHS Scotland patients beyond the life of the project for use in further projects, the options for this should be discussed with an accredited NHS Research Scotland biorespository where applicable. |

| | | | |
|---|---|---|---|
| 12.23 | ~~Under arrangements established in Scotland, each Health Board has a research tissue bank, accredited by Healthcare Improvement Scotland. With the exception of these banks, no other applications for REC review of research tissue banks should be made by researchers within NHS Scotland. Researchers working on NHS Scotland premises will be expected to utilise the accredited Health Board bank.~~ | | |
| 12.2~~7~~ (g) | Where a RTB in England, Wales or Northern Ireland has already obtained a licence from the HTA, a copy of the licence should be enclosed (it is not mandatory to have obtained the licence before applying for ethical review). | 12.26 (g) | Where a RTB in England, Wales or Northern Ireland has already obtained a licence from the HTA, a copy of the licence should be enclosed (it is not mandatory to have obtained the licence before applying for ethical review). In Scotland, the REC should inform the applicable accredited NHS Research Scotland biorepository about the application, which may need to be accompanied by a letter of support from the biorepository; |
| 12.3~~2~~ | In England, Wales and Northern Ireland the ethical review should generally complement the process of licensing by the HTA rather than duplicate it. RECs are not required to address governance issues that will be covered in detail in the licensing process. These include the suitability of the Designated Individual and other persons named on the licence, premises, facilities and equipment for storage of samples, donor identification and tracking systems, records of consent, security and risk management, arrangements for the disposal of samples, quality systems, internal/external audit, staff training. Although there is an ethical dimension to some of these issues, it is primarily | 12.31 | In England, Wales and Northern Ireland the ethical review should generally complement the process of licensing by the HTA rather than duplicate it. Similarly, in Scotland in relation to the Scottish accreditation scheme. RECs are not required to address governance issues that will be covered in detail in the licensing process. These include the suitability of the Designated Individual and other persons named on the licence, premises, facilities and equipment for storage of samples, donor identification and tracking systems, records of consent, security and risk management, arrangements for the disposal of samples, quality systems, internal/external audit, staff training. |

| | | | |
|---|---|---|---|
| | the responsibility of the HTA to set standards and ensure compliance ~~(this guidance does not apply in Scotland where there is no licensing process).~~ | | Although there is an ethical dimension to some of these issues, it is primarily the responsibility of the HTA to set standards and ensure compliance (in Scotland standards are assessed by the Scottish accreditation scheme for NHS Scotland biorepositories). |
| 12.3~~3~~ (b) | Except in Scotland or for RTBs not holding any relevant material, a copy of the licence from the HTA should be provided when available (if not already submitted). The REC should be notified if the Authority renews the licence, modifies the licensing conditions or revokes the licence, or of any change of Designated Individual | 12.32 (b) | Except in Scotland or for RTBs not holding any relevant material, a copy of the licence from the HTA should be provided when available (if not already submitted). The REC should be notified if the Authority renews the licence, modifies the licensing conditions or revokes the licence, or of any change of Designated Individual. In Scotland, the REC should inform the applicable accredited NHS Research Scotland biorepository about the application, which may need to include a letter of support from the biorepository. |
| 12.3~~7~~ (h) | Renewed approvals will normally be for a further period of 5 years, backdated to the end of the previous 5-year period. ~~Tissue banks based within NHS Scotland will not have their approval renewed. These banks come under the governance of the accredited Health Board.~~ | 12.36 (h) | Renewed approvals will normally be for a further period of 5 years, backdated to the end of the previous 5-year period. |
| ~~12.42~~ | ~~**Transitional arrangements for RTBs with an existing ethical approval**~~<br><br>~~Any ethical approval given by a REC to a RTB prior to 31 October 2006 lapsed on 30 October 2008. A new application may be made to a REC at any time.~~ | | |

| | | | |
|---|---|---|---|
| | | | |
| **Section 13: Research involving adults unable to consent for themselves** | | | |
| Para | SOP 7.4 | Para | SOP 7.5 |
| | References to Applications for Section 34 Approval and MCA2 Form have been removed | | |
| | References to the Mental Capacity Act (Northern Ireland 2016 have been added) and further clarity about reviewing arrangements made with regards to Northern Ireland and Scotland. | | |
| 13.15 (iii) | Processing of identifiable data outside the usual care team, where the research has (or will have) Section 251 ~~approval from the REC and the CAG (see Section 14 ).~~ | 13.15 (iii) | Processing of identifiable data outside the usual care team, where the research has (or will have) Section 251 <u>support</u> (not applicable to Northern Ireland)<u>. In Scotland the equivalent data will require to have Caldicott Guardian approval if held within a single Health Board or Public Benefit and Privacy Panel (PBPP) approval for data covering a number of Health Board areas or data held by Public Health Scotland.</u> |
| **Section 14: Communication with other regulators and review bodies** | | | |
| Para | SOP 7.3 | Para | SOP 7.4 |
| 14.3 | It is the responsibility of the sponsor to ensure where necessary that a research study has appropriate regulatory approval as well as a favourable ethical opinion before it starts. It is not necessary for evidence of regulatory | 14.3 | It is the responsibility of the sponsor to ensure where necessary that a research study has appropriate regulatory approval as well as a favourable ethical opinion before it starts. It is not necessary for evidence of regulatory |

| | | | |
|---|---|---|---|
| | approval to be provided to the REC before it confirms the final ethical opinion. ~~The Chief Investigator is requested to provide evidence of regulatory approval for the REC's records as soon as this is available, but it is not the responsibility of the REC to follow this up proactively.~~ | | approval to be provided to the REC before it confirms the final ethical opinion. |
| 14.1~~6~~ | The REC is required by the Clinical Trials Regulations to notify the MHRA of the final opinion, whether favourable or unfavourable, ~~so that it can be entered on EudraCT~~. The MHRA is notified automatically through its access to HARP. | 14.15 | The REC is required by the Clinical Trials Regulations to notify the MHRA of the final opinion, whether favourable or unfavourable. The MHRA is notified automatically through its access to HARP. |
| 14.1~~7~~ | ~~MHRA is also required to enter~~ the reasons for an unfavourable opinion in EudraCT, ~~using a checklist of standard fields prescribed by the European Commission (see Annex E).~~ This checklist is available within HARP. The Approvals Officer/REC Manager should provisionally complete the checklist within 2 working days of issuing the unfavourable opinion letter. The Approvals Manager should check that the fields have been completed appropriately, amend if necessary in discussion with the Approvals Officer/REC Manager and sign off for notification to MHRA in HARP within a further 3 working days. | 14.16 | The reasons for an unfavourable opinion in EudraCT. This checklist is available within HARP. The Approvals Officer/REC Manager should provisionally complete the checklist within 2 working days of issuing the unfavourable opinion letter. The Approvals Manager should check that the fields have been completed appropriately, amend if necessary in discussion with the Approvals Officer/REC Manager and sign off for notification to MHRA in HARP within a further 3 working days. |
| 14.2~~8~~ | Copies of inspection reports will not be routinely disclosed to RECs. However:<br>• Any report on a Phase 1 trial site will be provided to the REC or RECs ~~local to the site via RES;~~<br>• Reports will be disclosed in any case where regulatory or enforcement action is taken; | 14.27 | Copies of inspection reports will not be routinely disclosed to RECs. However:<br>• Any report on a Phase 1 trial site will be provided to the REC or RECs via the Quality and Performance Manager.<br>• Reports will be disclosed in any case where regulatory or enforcement action is taken; |

| | | | |
|---|---|---|---|
| | • Relevant information from other inspections (or copies of reports where appropriate) may be disclosed on request to the GCP Inspectorate from the REC or by the HRA. | | • Relevant information from other inspections (or copies of reports where appropriate) may be disclosed on request to the GCP Inspectorate from the REC or by the HRA. |
| 14.49 | The administration of radioactive substances in the United Kingdom is governed by the ~~Medicines (Administration of Radioactive Substances) Regulations 1978 (MARS), made under the Medicines Act 1968. Regulation 2 of MARS requires that any doctor or dentist wishing to administer radioactive medicinal products to humans should hold a certificate issued by Health Ministers. MARS also established the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise Health Ministers on the issuing of certificates.~~ ARSAC also provides advice on related matters, specifically those associated with radiological safety. The Secretariat to ARSAC is provided by a support unit within the Public Health England. | 14.48 | The administration of radioactive substances in the United Kingdom is governed by the Ionising Radiation (Medical Exposure) Regulations 2017 and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2018, (IR(ME)R). Regulation 5 of IR(ME)R requires that any doctor or dentist (referred to as a 'practitioner')wishing to administer radioactive medicinal products to humans must hold a licence issued by the Secretary of State in England, Health Ministers in Scotland and Wales or the Department of Health in Northern Ireland; their employer must also hold a valid licence. IR(ME)R authorises the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise the Secretary of State, Health Ministers and the Department of Health on the issuing of licences. ARSAC also provides advice on related matters, specifically those associated with radiological safety. The Secretariat to ARSAC is provided by a support unit within Public Health England. |
| 14.50 | Where research involves the administration of radioactive substances, additional to those provided as part of routine care, an ARSAC ~~research certificate~~ must be held at each research site where administrations take place. The certificate is site, procedure and holder specific. The issue of a ~~certificate~~ ("ARSAC research certificate") is required for any research involving administrations additional to | 14.49 | Where research involves the administration of radioactive substances, additional to those provided as part of routine care, an ARSAC licence must be held at each research site where administrations take place and by each practitioner responsible for administering research exposures. The issue of a licence ("ARSAC licence") is required for any research involving administrations |

| | | | |
|---|---|---|---|
| | those carried out by the certificate holder as part of normal clinical care. | | additional to those carried out by the licence holder as part of normal clinical care. |
| ~~14.51~~ | ~~Arrangements for collaboration between ARSAC and the Research Ethics Service have been agreed in a Memorandum of Understanding between RES and the Health Protection Agency.~~ | | |
| 14.5~~5~~ | Application to ARSAC is a two-stage process, comprising:<br><br>• A Preliminary Research Assessment (PRA) form, submitted by the sponsor's representative<br><br>• A Research Certificate Application (RCA) form, submitted by the local certificate-holder at the site if required. | 14.53 | Application to ARSAC is a two-stage process, comprising:<br><br>• A Preliminary Research Assessment (PRA) form, submitted by the sponsor's representative<br><br>• A new Employer Application Form and new Practitioner Application form can be submitted to obtain licences if these are not already held. ~~Research Certificate Application (RCA) form, submitted by the local certificate-holder at the site if required.~~ |
| 14.56 | Sponsors are encouraged to complete the PRA form within IRAS and submit parallel to the REC application booking to allow for early advice to be given by ARSAC to the sponsor on study-wide issues and for the REC to take account of this in the ethical review where appropriate. | 14.54 | Sponsors are encouraged to complete the PRA form within IRAS and submit parallel to the REC application booking with a copy of the Participant Information Sheet (PIS) to allow for early advice to be given by ARSAC to the sponsor on study-wide issues and for the REC to take account of this in the ethical review where appropriate. |
| 14.57 | ~~A Research Certificate Application (RCA) form may be submitted by the local certificate-holder as soon as both the REC application and the PRA form have been submitted. The form is submitted off-line, combined with other components of the ARSAC certificate application~~ | 14.55 | For individual research sites, study sponsors should notify the practitioner (for example, the nuclear medicine physician) and the employer under (IR(ME)R) about the research protocol during set-up, before any administrations take place at each medical radiological installation. |

| | | | |
|---|---|---|---|
| | ~~giving further details of the site and certificate-holder and including all necessary signatures.~~ | | Sponsors will be sent an approval document indicating which procedures have been approved. The Sponsor should provide the approval document to the practitioner and employer. |
| ~~14.60~~ | ~~Once ARSAC has received satisfactory responses from the sponsor's representative to any issues raised in the initial assessment, individual certificates will normally be issued within 2 working days of receipt of RCA forms unless further site-specific information is required. These do not normally require consultation with ARSAC members and will be processed within the ARSAC Support Unit.~~ | | |
| 14.61 | ~~Certificates~~ are not be copied to the REC office. It is the responsibility of the sponsor and the R&D office at the site to check that a certificate is in place before the study starts. | 14.58 | Licences are not to be copied to the REC office. It is the responsibility of the sponsor and the R&D office at the site to check that licenses are in place before the study starts. |
| 14.65 | Where a provisional opinion ~~letter~~ raises issues relevant to ARSAC's assessment, the ARSAC Support Unit may request sight of the CI's response. Otherwise, it is not necessary for the CI's response to be copied to ARSAC. | 14.62 | Where a provisional opinion raises issues relevant to ARSAC's assessment, the ARSAC Support Unit may request sight of the CI's response. Otherwise, it is not necessary for the CI's response to be copied to ARSAC. |
| **Section 15: Storage and retention of documentation** | | | |
| 15.7 | Separate detailed Operational Management Guidance is published relating to the closure of studies, archiving and destruction of application files. | | Separate detailed Operational Management Guidance along with the HRA Records Retention Schedule is published relating to the closure of studies, archiving and destruction of application files. |
| ~~15.9~~ | ~~Any remaining historic paper files, which have not been scanned to HARP or archived to CD or other electronic~~ | | |

| | | | |
|---|---|---|---|
| | ~~media, will normally be destroyed as soon as possible following the "retention date". Operational managers may exceptionally request to retain documentation where appropriate, for example, in the case of studies that are still the subject of complaints, investigations, insurance claims, or significant public or media interest.~~ | | |
| ~~15.~~ | ~~Further operational management guidance for RECs on the closure of studies is issued by the Head of Approvals Operations.~~ | | |
| ~~15.17~~ | ~~Where initial ethical review was undertaken by more than one REC prior to March 2004, there is no requirement to retain any documentation relating to ethical review undertaken by RECs other than the assigned REC for the study.~~ | | |
| **Annex A: Index to standard letters and forms** | | | |
| | **~~Forms for use by applicants (CTIMPs)~~**<br><br>~~A. Notification of amendment form (European Commission form)~~<br><br>~~B. Declaration of the end of a clinical trial (European Commission form)~~<br><br>~~C. Annual progress report form (RES)~~<br><br>~~D. Safety report form (RES)~~ | | |

| | | | |
|---|---|---|---|
| | ~~**Forms for use by applicants (non-CTIMPs)**~~<br><br>~~E. Declaration of the end of a study (RES)~~<br><br>~~F. Annual progress report (specific study) (RES)~~<br><br>~~G. Report of serious adverse event (RES)~~<br><br>~~H. Annual progress report (research tissue bank) (RES)~~<br><br>~~I. Annual progress report (research database) (RES)~~<br><br>~~Notices of substantial amendment should be submitted using IRAS with the exception of notice of substantial amendments to CTIMPS which can be submitted using the European amendment form (Annex II) All forms should be submitted to the REC by email.~~<br>~~Form B is Annex 3 to ENTR/CT1 issued by the European Commission. The form can be downloaded from the EudraCT website, see:~~<br>~~http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm~~ | | |
| | ~~**Site assessment**~~<br><br>~~SL23B Confirmation of favourable opinion for new NHS site following notice of substantial amendment in a CTIMP.~~ | | |

| | | | |
|---|---|---|---|
| | | | |
| **Annex C: Notification of Substantial Amendments to CTIMPs** | | | |
| | **Amendments normally requiring a favourable ethical opinion only**<br><br>Significant increase to the radiation exposures to ~~subjects~~ from the protocol. | | **Amendments normally requiring a favourable ethical opinion only**<br><br>Significant increase <u>or decrease</u> to the radiation exposures to <u>participants</u> from the protocol. |
| | **Amendments normally requiring a favourable ethical opinion only**<br><br>• Significant changes to participant information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, etc. (whether generic to the whole study or specific to a particular trial site).<br>• Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial.<br>• Significant increase to the radiation exposures to subjects from the protocol.<br>• Change of insurance or indemnity arrangements for the trial.<br>• Change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.<br>• Change of the Chief Investigator. | | **Amendments normally requiring a favourable ethical opinion only**<br><br>• Significant changes to participant information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, etc. (whether generic to the whole study or specific to a particular trial site).<br>• Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial.<br>• Significant increase to the radiation exposures to subjects from the protocol.<br>• Change of insurance or indemnity arrangements for the trial.<br>• Change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator.<br>• Change of the Chief Investigator. |

| | | | |
|---|---|---|---|
| | • Change of Principal Investigator at a trial site.<br>• Addition of new trial sites not listed with the original request for authorisation and REC application.<br>• Change to the definition of a trial site.<br>• Any other significant change to the conduct or management of the trial at particular trial sites.<br>• Any other significant change to the terms of the original REC application. | | • Change of Principal Investigator at a non-NHS/HSC trial site.<br>• Addition of new non-NHS/HSC trial sites not listed with the original request for authorisation and REC application.<br>• Change to the definition of a trial site.<br>• Any other significant change to the conduct or management of the trial at particular trial sites.<br>• Any other significant change to the terms of the original REC application. |
| | **Amendments not normally requiring notification as substantial amendments**<br><br>• Changes to the identification of the trial (e.g. change of title).<br>• Increase in duration of the trial, provided that the exposure to treatment is not extended, the definition of the end of trial is unchanged and there is no change to monitoring arrangements.<br>• Changes to the numbers of participants planned in the UK as a whole or at individual trial sites, provided that there is no change to the total number of participants in the trial or the increase/decrease is insignificant in relation to the overall sample size.<br>• Change in the documentation used by the research team to record study data (e.g. case report form or data collection form).<br>• Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis.<br>• Changes to the research team other than to Chief or ~~Principal Investigators.~~ | | **Amendments not normally requiring notification as substantial amendments**<br><br>• Changes to the identification of the trial (e.g. change of title).<br>• Increase in duration of the trial, provided that the exposure to treatment is not extended, the definition of the end of trial is unchanged and there is no change to monitoring arrangements.<br>• Changes to the numbers of participants planned in the UK as a whole or at individual trial sites, provided that there is no change to the total number of participants in the trial or the increase/decrease is insignificant in relation to the overall sample size.<br>• Change in the documentation used by the research team to record study data (e.g. case report form or data collection form).<br>• Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis.<br>• Changes to the research team other than to Chief Investigators. |

| | | | |
|---|---|---|---|
| | • Changes to contact details.<br>• Changes to the internal organisation of the sponsor or persons to whom tasks have been delegated.<br>• Changes to the logistical arrangements for transporting or storing samples.<br>• Changes to technical equipment.<br>• Inclusion or withdrawal of another Member State or third country.<br>• Non-significant clarifications of the protocol.<br>• Non-significant clarifications or updates of participant information documentation.<br>• Corrections of typographical errors.<br>• Participant information regarding post trial arrangements where this does not contradict what is stated in the protocol.<br><br>The issue of an updated Investigator's Brochure or Summary of Medicinal Product Characteristics for the IMP is not itself regarded as a substantial amendment unless it includes changes that would meet the criteria for a substantial amendment. There is no requirement to provide the MHRA or REC with updated versions of the Investigator's Brochure or SMPC routinely or to seek authorisation or an ethical opinion. | | • Changes to contact details.<br>• Changes to the internal organisation of the sponsor or persons to whom tasks have been delegated.<br>• Changes to the logistical arrangements for transporting or storing samples.<br>• Changes to technical equipment.<br>• Inclusion or withdrawal of another Member State or third country.<br>• Non-significant clarifications of the protocol.<br>• Non-significant clarifications or updates of participant information documentation.<br>• Corrections of typographical errors.<br>• Participant information regarding post trial arrangements where this does not contradict what is stated in the protocol.<br><br>The issue of an updated Investigator's Brochure or Summary of Medicinal Product Characteristics for the IMP is not itself regarded as a substantial amendment unless it includes changes that would meet the criteria for a substantial amendment. There is no requirement to provide the MHRA or REC with updated versions of the Investigator's Brochure or SMPC routinely or to seek authorisation or an ethical opinion. |

| Annex D: Corrective procedures following a legally invalid ethical opinion on a CTIMP | | | |
|---|---|---|---|
| 3. | Any information relating to a possible invalid ethical opinion should initially be sent to the Operational Manager for further investigation. If it is confirmed that there has been non-compliance, the Operational Manager (in England this will be the Head of Approvals Support) will take the following action as soon as possible:<br><br>(i) Initiate corrective action to ensure the trial has a valid ethical opinion, following further review of the trial where appropriate;<br><br>(ii) Notify the Clinical Trials Unit and the GCP Inspectorate of the non-compliance and the corrective action being taken by the Research Ethics Service; and<br><br>(iii) Notify the sponsor and give advice about the action it should take. | 3. | Any information relating to a possible invalid ethical opinion should initially be sent to the Approvals Officer/REC Manager for further investigation. If it is confirmed that there has been non-compliance, the Operational Manager (in England this will be the Head of Approvals Support) will take the following action as soon as possible:<br><br>(i) Initiate corrective action to ensure the trial has a valid ethical opinion, following further review of the trial where appropriate;<br><br>(ii) Notify the Clinical Trials Unit and the GCP Inspectorate of the non-compliance within 7 days of the matter coming to their attention and the corrective action being taken by the Research Ethics Service as a follow up report; and<br><br>(iii) Notify the sponsor and give advice about the action it should take. |
| 5.1 | **Trial submitted as a CTIMP and favourable opinion given by non-recognised committee**<br><br>If a Trial is submitted as a CTIMP and a favourable opinion is given by non- recognised committee: | | **Trial submitted as a CTIMP and favourable opinion given by non-recognised committee or without the appropriate type of recognition** |

| | | | |
|---|---|---|---|
| | (i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants ~~and prepare a new application for review by an ethics committee with appropriate recognition.~~<br>(ii) The Operational Manager should identify an appropriate committee, secure an early agenda slot and notify the sponsor of the submission arrangements.<br>(iii) The sponsor should submit a substantial amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.<br>(iv) When a new favourable opinion is obtained, the sponsor should submit a further Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.<br>(v) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice. | 5.1 | If a Trial is submitted as a CTIMP and a favourable opinion is given by non- recognised committee or a committee without the appropriate type of recognition:<br><br>(i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants.<br>(ii) The Operational Manager should identify an appropriate committee, secure an early agenda slot, transfer the application to the second committee and notify the sponsor of the submission arrangements.<br>(iii) The Operational Manager should notify the MHRA within 7 days of the matter coming to the attention of the REC and confirm the corrective action taken in a follow up report.<br>(iv) The sponsor should submit a substantial amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.<br>(v) When a new favourable opinion is obtained, the sponsor should submit a further Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.<br>(vi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice. |

| | | | |
|---|---|---|---|
| ~~5.2~~ | ~~**Trial submitted as a CTIMP and favourable opinion given by a committee without appropriate type of recognition**~~<br>~~If a Trial is submitted as a CTIMP and a favourable opinion given by a committee without the appropriate type of recognition:~~<br>~~(i) The sponsor should suspend all trial activity as soon as possible, except where this would be detrimental to the health of participants and prepare a new application for review by an ethics committee with appropriate recognition.~~<br>~~(ii) The Operational Manager will identify an appropriate committee, secure an early agenda slot and notify the sponsor of the submission arrangements.~~<br>~~(iii) The sponsor should submit a Substantial Amendment to the MHRA, notifying voluntary suspension of the trial and the corrective action being taken.~~<br>~~(iv) When a new favourable opinion is obtained, the sponsor should submit a further Substantial Amendment to the MHRA, seeking authorisation to re-start the trial. Consideration should be given to seeking fresh consent from subjects.~~<br>~~(vi) If the MHRA does not receive notification of voluntary suspension, it will consider issuing a suspension notice.~~ | | |

| | | | |
|---|---|---|---|
| ~~5.4~~ | ~~**Trial with ethical opinion from a type ii committee extended to another domain without review by a type iii committee**~~<br><br>~~5.4 If a Trial with an ethical opinion from a type ii committee is extended to another domain without review by a type iii committee:~~<br>~~(i) The Head of Approvals Support will seek early approval from UKECA in correspondence to change the terms of the ethics committee's recognition to type iii for the purposes of this trial only.~~<br><br>~~(ii) Once UKECA approval is obtained, the operational manager will notify the Clinical Trials Unit and GCP Inspectorate of the non-compliance and the corrective action taken.~~<br><br>~~(iii) There is generally no need to notify the sponsor or for the trial to be suspended.~~<br><br>~~(iv) If, exceptionally, UKECA approval is not given, further corrective action should be taken in the same way as for a trial without an opinion from an appropriately recognised committee.~~ | | |
| | **Where the trial was reviewed by a non-recognised committee** | | **Where the trial was reviewed by a non-recognised committee <u>or without the appropriate type of recognition</u>** |

| | | | |
|---|---|---|---|
| | (xi) The procedures under 5.1 apply.<br><br>**~~Where the trial was reviewed by a committee without appropriate recognition for the type of CTIMP~~**<br><br>~~(xii) The procedures under 5.2 apply.~~ | | (xi) The procedures under 5.1 apply. |
| 5.~~5~~ | If a Trial is non-compliant with requirements of Regulation 15 or Schedule 217:<br><br>(i) ~~The Head of Approvals Operations~~ should investigate further and consider whether there is any reason to be concerned about the safety or well-being of the trial subjects taking into account the nature and extent of the non-compliance.<br><br>**Where no concerns arise:**<br>(ii) The Head of Approvals ~~Operations~~ will make arrangements for the ethics committee to re-consider the application and confirm its opinion at a quorate meeting as soon as possible.<br>(iii) When the opinion is confirmed, the Head of Approvals ~~Operations~~ will notify the sponsor of the non-compliance | 5.3 | If a Trial is non-compliant with requirements of Regulation 15 or Schedule 217:<br><br>(i) The Operational Manager (in England this will be the Head of Approvals Support) should investigate further and consider whether there is any reason to be concerned about the safety or well-being of the trial subjects taking into account the nature and extent of the non-compliance. The Operational Manager should notify the MHRA, of the non-compliance within 7 days of the matter coming to the attention of the REC and notify the MHRA the corrective action taken in a follow up report.<br><br>**Where no concerns arise:**<br>(ii) The Head of Approvals Support will make arrangements for the ethics committee to re-consider the application and confirm its opinion at a quorate meeting and to ascertain if the non-compliance was related to Regulation 15 after seeking appropriate expert advice, as soon as possible. |

| | | | |
|---|---|---|---|
| | and the corrective action taken and arrange for revised documentation to be issued.<br><br>(iv) The Head of Approvals ~~Operations~~ will confirm to the Clinical Trials Unit that corrective action has been taken. | | (iii) When the opinion is confirmed, the Head of Approvals Support will notify the sponsor of the non-compliance and the corrective action taken and arrange for revised documentation to be issued.<br><br>(iv) The Head of Approvals Support will confirm to the Clinical Trials Unit that corrective action has been taken, with a follow up report to the initial breach report. |
| **ANNEX E: Notification of reasons for unfavourable opinion to the MHRA** | | | |
| | ~~1.The EudraCT database includes a list of prescribed fields to record the reasons for an unfavourable opinion given by an ethics committee on a CTIMP. (See European Commission document at http://ec.europa.eu/health/files/eudralex/vol-10/2010_10_14_final.pdf ). This information is available within the closed module of EudraCT to all Competent Authorities in EU Member States. It is not publicly available except in the case of paediatric clinical trials, for which the reasons will be published along with other details of the trial at www.ClinicalTrialsRegister.eu.~~<br><br>~~2. The checklist of fields in EudraCT is as follows:~~<br><br>~~• Relevance of the clinical trial.~~<br><br>~~• Evaluation of the anticipated benefits and risks.~~ | | 1.The checklist is completed in HARP when issuing an unfavourable opinion in a CTIMP and made available electronically to the MHRA (see paragraph 14.15-14.17 of SOPs). |

| | | | |
|---|---|---|---|
| | ~~• Investigators and staff.~~<br>~~• Facility in a single-centre trial.~~<br>~~• All facilities in a multi-centre trial.~~<br>~~• Inclusion and exclusion criteria.~~<br>~~• Control group.~~<br>~~• Recruitment procedures.~~<br>~~• Participant Information Sheet and consent form and procedure.~~<br>~~• Measures to minimise pain, discomfort and fear.~~<br>~~• Insurance and/or indemnity (for liability) or no fault compensation in the event of injury or death attributable to the trial.~~<br>~~• Compensations (i.e. payments/rewards) to participants) to investigators.~~<br>~~• Agreement between sponsor and site relevant to compensations to participants or investigators.~~<br>~~• Inclusion of persons incapable of giving informed consent or other vulnerable populations.~~<br>~~• Data protection and confidentiality.~~<br>~~• Compliance with GCP.~~<br>~~• Fulfilment of administrative requirements.~~<br>~~• Other.~~ | | |

| | | | |
|---|---|---|---|
| | 3. The checklist is completed in HARP when issuing an unfavourable opinion in a CTIMP and made available electronically to the MHRA (see paragraph 14.16-14.18 of SOPs). | | |
| **~~Annex F: Format and Content of Annual Safety Reports on CTIMPs~~** | | | |
| | ~~The ICH E2F guideline on Development Safety Update Reports, which establishes the standards for annual safety reports required under the EU Clinical Trials Directive, recommends that reports should adopt the format set out below. For each heading where information is available, the information should be presented concisely. Where no information is available, or the section is not applicable, this should be stated.~~<br>**~~Table of contents~~**<br>**~~Title page~~**<br>**~~Executive Summary~~**<br>~~1. Introduction~~<br>~~2. Worldwide marketing approval status~~<br>~~3. Actions taken in the reporting period for safety reasons~~<br>~~4. Changes to reference safety information~~ | | |

| | | | |
|---|---|---|---|
| | ~~5. Inventory of clinical trials ongoing and completed during the reporting period~~<br>~~6. Estimated cumulative exposure~~<br>~~6.1 Cumulative subject exposure in the development programme~~<br>~~6.2 Patient exposure from marketing experience~~<br>~~7. Data in line listings and summary tabulations~~<br>~~7.1 Reference information~~<br>~~7.2 Line listings of serious adverse reactions during the reporting period~~<br>~~7.3 Cumulative summary tabulations of serious adverse events~~<br>~~8. Significant findings from clinical trials during the reporting period~~<br>~~8.1 Completed clinical trials~~<br>~~8.2 Ongoing clinical trials~~<br>~~8.3 Long-term follow-up~~<br>~~8.4 Other therapeutic use of investigational drug~~<br>~~8.5 New safety data related to combination therapies~~ | | |

| | | | |
|---|---|---|---|
| | ~~9. Safety findings from non-interventional studies~~<br>~~10. Other clinical trial / study safety information~~<br>~~11. Safety findings from marketing experience~~<br>~~12. Non-clinical data~~<br>~~13. Literature~~<br>~~14. Other DSURs~~<br>~~15. Lack of efficacy~~<br>~~16. Region-specific information~~<br>~~17. Late-breaking information~~<br>~~18. Overall safety assessment~~<br>~~18.1 Evaluation of the risks~~<br>~~18.2 Benefit-risk considerations~~<br>~~19. Summary of important risks~~<br>~~20. Conclusions~~<br>~~Appendices to the DSUR~~<br>**~~Title page~~**<br>~~The title page of the DSUR should include the following information:~~ | | |

| | | | |
|---|---|---|---|
| | ~~• DSUR number (reports should be numbered sequentially)~~<br>~~• Investigational drug~~<br>~~• Reporting period~~<br>~~• Date of the report~~<br>~~• Sponsor name(s) and address(es)~~<br>~~• Statement on the confidentiality of the information included in the DSUR~~<br>~~• A cautionary statement that the DSUR includes unblinded information, if applicable~~<br><br>~~**Executive Summary**~~<br><br>~~This section should provide a concise summary of the important information in the report, suitable for review by REC members as a stand-alone document.~~<br><br>~~The following information should be included in the Executive Summary:~~<br>~~• Introduction – report number and reporting period~~<br>~~• Investigational drug(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s)~~ | | |

| | | | |
|---|---|---|---|
| | ~~• Estimated cumulative exposure of clinical trial subjects~~<br>~~• Marketing approval(s) (yes/no) – if yes, number of countries~~<br>~~• Summary of overall safety assessment (based on section 18 of the DSUR)~~<br>~~• Actions taken for safety reasons including significant changes to the IB~~<br>~~• Conclusions~~<br>~~Further detailed guidance on each section of the DSUR is available within the ICH E2F guideline, available at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm~~ | | |
| **Annex F: Insurance, Indemnity and Compensation (was previously Annex G)** | | | |
| | ~~**Validation of applications**~~<br><br>~~31.As part of the validation requirements, staff should check that the Statement of Insurance Cover has been completed in IRAS - there is no need for a further signature as the necessary assurance is provided by the sponsor representative declaration in Part D of IRAS.~~<br><br>~~32. It is strongly recommended that a copy of the insurance certificate is also submitted with the initial~~ | | |

| | | | |
|---|---|---|---|
| | ~~application, but applications may be validated without a copy of the certificate on the understanding that a copy is provided as soon as possible and in any event before the start of the trial. Where not received at the time of issuing a favourable opinion, the REC should attach a condition to its opinion to require that the certificate is provided.~~ | | |