CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS IN HUMAN SUBJECTS

After ethical review – guidance for sponsors and investigators

This document sets out important guidance for sponsors and investigators on the conduct and management of Clinical Trials of Investigational Medicinal Products (CTIMPs) following ethical review. The guidance is supplementary to the ethical opinion provided in the letter from the Research Ethics Committee. However, some reporting procedures described below are statutory requirements under the Medicines for Human Use (Clinical Trials) Regulations 2004 ("The Regulations"); this is indicated in the text. Failure to comply with these requirements could lead to the Research Ethics Committee recommending to the Medicines and Healthcare products Regulatory Agency (MHRA) that the clinical trial authorisation should be suspended or terminated.

This document should be read in conjunction with the UK Policy Framework for Health and Social Care Research which sets out principles of good practice in the management and conduct of health and social care research in the UK including responsibilities for the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

1. Further communications with the Research Ethics Committee

1.1 Further communications during the trial with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as "the REC") are generally the responsibility of the lead sponsor. However, the sponsor may delegate responsibility to the Chief Investigator or another representative.

1.2 Where there is more than one sponsor for the trial, it is recommended that the lead sponsor or its representative takes responsibility for all communications with the REC. However, one of the co-sponsors or joint sponsors may take responsibility for each of the following group of functions:

- Substantial amendments, non-substantial amendments, modified amendments and the conclusion of the trial
- Urgent safety measures
- Pharmacovigilance reporting.

2. Registration

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant.

Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

For CTIMPs involving both UK and EU sites a record in the EU Clinical Trials Register (other than adult Phase 1 studies) will exist and will satisfy the requirement for registration.

For CTIMPs only taking place in the UK sponsors must register the trial on an established international registry which is a Primary Registry listed in the WHO Registry Network or the ICMJE list of registries e.g. the ISRCTN registry or ClinicalTrials.gov.

You should notify *both* the REC and the MHRA of the registration details.

Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

3. Commencement of the trial

3.1 It is assumed that the trial will commence (i.e. the initiation of any protocol procedures) within 12 months of the date of the favourable ethical opinion.

3.2 Under the Regulations the sponsor must obtain Clinical Trial Authorisation (CTA) from the MHRA before commencement of the trial. Evidence of the CTA should be forwarded when available (if not already provided to the REC). Where the MHRA requests significant changes to the protocol before confirming CTA, or attaches any other condition requiring substantial amendments to be made to the terms of the REC application or the supporting documentation, a Substantial Amendment must be submitted. (see section 7).

3.3 The trial should not commence at any site until management permission has been obtained from the organisation responsible for the care of the participants at the site.

3.4 Should the trial not commence within 12 months of the favourable opinion being issued; the sponsor should send the REC a written explanation for the delay. A further written explanation should be sent after 24 months if the research has still not commenced.

3.5 Should the trial not commence within 24 months of the favourable opinion being issued, the REC may recommend to the MHRA that the CTA should be suspended or terminated.

4. The Over-Volunteering Prevention System (TOPS)

For Phase 1 studies involving healthy volunteers, the sponsor is expected to ensure that all participants enrolled into the study are registered with The Over-Volunteering Prevention System (TOPS).

5. Duration of ethical opinion

5.1 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, subject to approved substantial amendments. 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.

5.2 The favourable ethical opinion provides legal authority to hold "relevant material" for research on premises which are not licensed by the Human Tissue Authority (in England, Northern Ireland and Wales only – this requirement does not apply in Scotland). Where a favourable ethical opinion provides this legal authority, "relevant material" can be held under the terms of the ethical opinion until the end of the period declared in the application; and approved by the REC.

5.3 **Samples may be held 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 a defined period of time (and no longer than 12 months). After this period legal authority to hold any "relevant material" for this project on premises which are not licensed by the Human Tissue Authority will expire (in England, Northern Ireland and Wales only - this requirement does not apply in Scotland). To ensure that any continued storage of "relevant material" for this project is lawful (in England, Northern Ireland or Wales), 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 the existing project expires. Otherwise the tissue would need to be destroyed in accordance with the HTA Codes of Practice and Standards on Research (code E).

6. Progress reports

6.1 Research Ethics Committees can review a favourable opinion in the light of progress reports and any developments relevant to the trial. The Chief Investigator is responsible for ensuring the research remains scientifically sound, safe, ethical, legal and feasible throughout its duration. The Chief Investigator should submit a progress report to the REC 13 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter until the end of the trial is declared.

6.2 Progress reports should be in the format prescribed by the HRA and published on the website at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

7. Amendments

7.1 If the sponsor proposes to make a substantial amendment to the clinical trial authorisation, the Regulations require that a substantial amendment must be submitted to the REC and/or the MHRA (as appropriate).

7.2 A substantial amendment is any amendment to the terms of the request for clinical trial authorisation, or to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the REC that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial participants

(b) the scientific value of the trial

(c) the conduct or management of the trial

(d) the quality or safety of any investigational medicinal product used in the trial.

7.3 Notices of Amendment should be submitted through IRAS. 6.4 A substantial amendment on which an ethical opinion has been requested must not be implemented until a favourable ethical opinion has been given by the REC, unless the changes to the trial are urgent safety measures (see section 9). The REC is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

7.5 Amendments that are not substantial amendments may be made at any time and do not need to be notified to the REC. Notifying the REC of changes to the contact details for the research team and study sponsor is strongly encouraged.

7.6 Further guidance on amendments is available in IRAS help:
https://www.myresearchproject.org.uk/help/hlpamendments.aspx

8. Changes to Sites

8.1 A substantial amendment should be submitted to the REC where it is proposed to:

- include a new site in the trial, not included in the list of proposed trial sites in the original REC application and request for CTA
- appoint a new PI at a trial site
- make any other significant change to the conduct or management of a trial site

NHS sites

8.2 For all changes at NHS/HSC sites, the REC will normally acknowledge receipt and confirm ethical approval on the condition that confirmation of capacity and capability (in England, Northern Ireland and Wales) or NHS Management Permission (in Scotland) is obtained prior to any research project activity commencing at the site.

Non-NHS sites

8.3 Changes at non-NHS/HSC sites require submission of the non-NHS/HSC Site Assessment Form along with a substantial amendment and the relevant supporting documentation.

Guidance on how to work with sites is provided in the IRAS help section at:
https://www.myresearchproject.org.uk/help/hlpsitespecific.aspx

9. Urgent safety measures

9.1 The sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect the trial participants against any immediate hazard to their health or safety.

9.2 The Regulations require that the REC and the MHRA must be notified within 3 days that such measures have been taken, the reasons why and the plan for further action.

10. Pharmacovigilance

10.1 Safety reporting requirements are set out in "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials of medicinal products for human use" (CT3) issued by the European Commission and available at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm Guidance is also available on the HRA website.

10.2 Under the Regulations, Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the trial in the UK must be notified to the Committee and the MHRA in expedited fashion. A SUSAR which is fatal or life-threatening must be reported as soon as possible and in any event within 7 days after the sponsor became aware of the event. Any additional relevant information must be reported within 8 days of sending the first report. A SUSAR which is not fatal or life-threatening must be reported as soon as possible and in any event within 15 days after the sponsor first became aware of the event.

10.3 There is no requirement to notify SUSARs occurring in the trial outside the UK or in other trials of the investigational medicinal product (IMP).

10.4 There is no requirement to notify serious adverse events occurring in the trial, other than SUSARs.

10.5 For each IMP being tested in the trial, the Regulations require the sponsor to provide the REC and the MHRA with an annual safety report of the safety of the subjects in clinical trials of the IMP for which it is the sponsor (whether in the UK or elsewhere). The report should be provided in the format for Development Safety Update Reports (DSURs) set out in the ICH E2F standard available from the Commission website http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf or at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

The DSUR should include an aggregated global listing of all Suspected Serious Adverse Reactions (SSARs) occurring in the relevant trials in the reporting period.

10.6 In the case of double blind trials, un-blinding should take place before reporting adverse reactions.

10.7 Pharmacovigilance reports may be provided to the REC by either the sponsor, or the sponsor's representative, or the Chief Investigator. All reports should be sent by email or using other electronic media. Reports should be accompanied by the cover sheet for safety reports published on the HRA website. A single cover sheet may be used for the submission of several reports.

10.8 Phase 1 studies in Healthy Volunteers and Patients

For Phase 1 studies in healthy volunteers or patients, it is expected that the accuracy of any data used to make major safety decisions, including dose escalation decisions will be ensured via quality

control (QC) processes (either by the unit or by sponsor monitoring) including pharmacokinetic (PK) or pharmacodynamic (PD) data especially those that that are linked to protocol stopping criteria. There should be a dose escalation process where the Principal Investigator(s) and the sponsor review all the data required as specified in the protocol and make a documented decision.

11. Conclusion or early termination of the trial

11.1 Under the Regulations, the sponsor must notify the REC and the MHRA in writing that the trial has ended within 90 days of the conclusion of the research. Unless otherwise specified in the protocol, the conclusion of the trial is normally defined as the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. Any change to the definition of the conclusion of the trial should be notified to the Committee and the MHRA as a substantial amendment.

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

11.3 Declarations of conclusion or early termination should be on the form issued by the European Commission at Annex 3 to the CT1 guidance.

12. Final report

12.1 A final report on the research should be provided within 12 months of the conclusion of the study.

13. Reporting results

13.1 Other than early phase trials, the findings, whether positive or negative, should be made accessible within one year of the end of trial in the public register (or registers) where you have registered your clinical trial. If the register used does not have a results section, the results should be posted on a free-to-access, publicly available, searchable institutional website of the sponsor, funder or chief investigator.

13.2 Where the main findings are also to be submitted for publication in a journal, this should be done within 12 months of study completion, to be published through an open-access mechanism in a peer-reviewed journal.

13.3 Where appropriate, information about the findings of the research should be made available, in a suitable format and timely manner, to those who took part in it, unless otherwise justified.

14. Review of ethical opinion

14.1 The REC may review its opinion at any time in the light of any relevant information it receives. It has no power to legally withdraw the opinion it has given but may draw the attention of the MHRA to any serious concerns and may recommend that consideration is given to suspending or terminating the CTA.

14.2 The sponsor or Chief Investigator may at any time request that the REC reviews its opinion, or seek advice from the REC on any ethical issue relating to the trial.

15. Serious breaches of Good Clinical Practice or the protocol

15.1 Under the Regulations the sponsor must notify the MHRA of any serious breach of the conditions or principles of Good Clinical Practice (GCP) or of the protocol, within 7 days of the matter coming to its attention. A breach should be regarded as serious if it is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. It is requested that the sponsor should also notify the REC of such breaches within the same timescale. There is no requirement to notify minor breaches of GCP or the protocol.

15.2 A minor deviation from the protocol to deal with unforeseen circumstances should be exceptional and is not considered to be a serious breach of the protocol provided that it is approved by the Chief Investigator, either in advance or after the event. However, if the deviation would meet the criteria for a substantial amendment it must be notified to the REC under the Regulations.

15.3 There is no statutory provision for the REC to approve proposed deviations from the protocol for individual subjects. It is the responsibility of the sponsor to consider whether protocol amendments should be made in such cases. Where the amendment is substantial, it must be notified.

16. Long Term Studies

The sponsor and Chief Investigator are responsible for ensuring that the study procedures and documentation are updated in light of legislative or policy changes and also for reasons of good practice (e.g. standards for supporting documentation). This should be documented in the progress report to the REC (see above) and, where necessary, an amendment (see above) should be submitted to the REC. The REC may review its opinion in light of legislative changes or other relevant developments.