UNIVERSITY OF SUSSEX

Standard Operating Procedures for Close Out of a CTIMP

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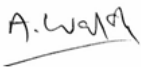
Author: Antony Walsh **Designation:** RES Research Governance Officer	*Signature* 	*Date* 25 August 2020
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[1] http://www.sussex.ac.uk/staff/research/governance

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1. Purpose & Scope

1.1 The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union (EU). It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document[2].

1.2 This SOP describes the procedures to be undertaken when a University of Sussex (US) sponsored Clinical Trials of Investigational Medicinal Product (CTIMP) ends.

1.3 The scope of the document is for all schools at the US, all members of staff with substantive employment and students registered at the University (including Brighton and Sussex Medical School (BSMS)) undertaking CTIMPs. The scope of the document includes anyone undertaking activities for a Clinical Trial on behalf of the University.

2. Introduction

2.1 Close out is defined as the process of ensuring that all trial related activities are appropriately managed, reconciled and reported at the end of a study in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care (HSC) Research.

2.2 Close out is integral to the quality of a study and is designed to ensure that all necessary documents are in place and that data is complete, should it be necessary for the study documentation to be retrieved or audited by the sponsor or inspected by the regulatory authority(ies) in the future.

2.3 The objective of trial close-out is to ensure that:

- The rights and wellbeing of all participants are protected
- All essential documents have been stored appropriately in the Trial Master File (TMF) and Investigator Site Files (ISF)
- The correct approved version of the protocol was used and adhered to
- IMP (Investigational Medicinal Product) accountability has been carried out
- Any SAEs (Suspected Adverse Events), and SUSARs (Suspected Unexpected Serious Adverse Reactions) have been reported appropriately
- DSURs (Development Safety Update Reports) have been submitted
- Source Data Verification (SDV) has been undertaken
- Monitoring has been performed as described in the study monitoring plan
- All contractual requirements have been met
- Any outstanding queries between the Sponsor and sites are resolved

- A study close-out report is produced and submitted to the Sponsor

3. Responsibilities

Sponsor

3.1 The Sponsor is responsible for:

- Approving the definition of what will constitute the end of study in the study protocol.
- Approvals to close the study and to ensure that the results are published / disseminated appropriately.
- Maintaining the relevant database/s with the end date and study status related to closure or extension based on information from the Chief Investigator (CI) and set reminders for final reports
- Ensuring that all relevant parties are informed within the required timelines.
- Finalising the study files ensuring all necessary documents are present in TMFs / ISFs and ensuring all end of study procedures are completed.

Chief Investigator (CI)

3.2 The Chief Investigator is responsible for:

- Ensuring the definition of the 'End of Trial' is included in the protocol (see SOPRG01 - Sponsorship approval CTIMPs)
- Taking into account the protocol, the CI shall determine whether the study:
  - Is due to conclude as described in the study protocol; *OR*
  - Requires an extension to the end date; *OR*
  - Is to terminate early, and why
- Discussing with the Sponsor regarding the study conclusion or extension requirement.
- Completing required documentation.
- Informing the regulatory authorities and the REC (Research Ethics Committee), and all other relevant parties as necessary copying in the Sponsor to all correspondence.

4. Procedure

4.1 Planned Closure

4.1.1 It is expected that the definition of planned trial closure will be outlined in the study protocol. The end of study will usually be defined as the last visit of the last patient or the final follow-up

completion and data collection. In the event that closure occurs prior to the planned date, specific requirements, set out in sections 4.6 below will also apply.

4.2 Recruitment Closure

4.2.1 The following shall be undertaken to ensure the closure of recruitment for a CTIMP:

- Recruitment closure must be planned and agreed with the study teams.
- Relevant organisations involved in the study (e.g. funders etc.) shall be notified of the closure to recruitment.
- An official confirmation of recruitment closure must be sent to each site at the appropriate time
- Relevant study registries such as ISRCTN (International Standard Randomised Controlled Trial Number) Registry , ClinicalTrials.gov and study websites must be updated to confirm recruitment closure.
- Internal University Sponsorship spreadsheets and records must be updated.

4.3 Closure of a participating investigational site(s)

4.3.1 For each trial site, the following tasks must be completed before official study closure:

- All data entry onto the CRFs (Case report forms) must be complete and queries must be resolved.
- If applicable, the final Electronic Data Capture (EDC) output must be printed or saved onto a CD/DVD and filed in the ISF.
- All Serious Adverse Events must be fully documented, and any unresolved adverse events followed up where required,
- All laboratory documentation must be collated with the main Investigator Site File and shipping/destruction of samples completed as required.
- The Declaration of the end of a study form, including evidence of notifying local R&D department must be added to the ISF.
- Any unused study-related supplies and materials must be retrieved, returned, or authorised for destruction where required.
- All sections of the ISF must be collated ready for archiving.

4.3.2 Once the site can be closed, a formal site closure notification will be sent to the investigator to confirm that the site is closed and that study related documents can be archived.

4.3.3 A completed Closedown Site Checklist must also be completed and submitted to research sponsorship@sussex.ac.uk for each site.

4.4 Formal notification to the Research Ethics Committee (REC) and other bodies

4.4.1 At the end of the trial, the CI must notify the REC that gave them a favourable opinion, the MHRA and the R&D offices of NHS research sites that the study has ended. This must be done using the 'Declaration of the End of a study form' accessed via the MHRA's web pages:

http://ec.europa.eu/health/files/eudralex/vol-10/declaration_end_trial_form.doc

This must be done within 90 days of the end of the study.

4.4.2 Prior to completing the 'Declaration of the End of a Study', the Chief Investigator should review the plans that had been approved by the REC for use of tissue and data collected in the course of the study, providing information to participants, and the dissemination of results. Any need to make changes to these approved arrangements (through submission of a substantial amendment) should be identified and actioned prior to submission of the 'Declaration of the End of a Study' form.

4.4.3 A final Clinical Study report must be submitted with 12 months of the end of the study. There is no standard format for this but must include as a minimum, whether the study achieved its objectives, what the main findings were and the arrangements for publication/dissemination of the research.

4.4.4 A copy of both the 'Declaration of the End of a Study form' and a copy of the final Clinical Study report must also be provided to the sponsor by emailing:

researchsponsorship@sussex.ac.uk. Any other relevant parties must also be notified e.g. funders.

4.5 Overall Study Closure

4.5.1 Once all the data from sites has been received and no more queries remain, a copy of the database must be sent for analysis according to the protocol. The final analysis of the data (following 'lock' of the study database) and report writing is expected to occur after formal declaration of the end of the study.

4.5.2 A copy of the database sent for analysis must be filed in the TMF.

4.5.3 Once analysis has been completed, approval to archive may be sent to study sites.
A statistical analysis report must be prepared and a copy filed in the TMF Publications will be prepared according to the protocol.

4.5.4 Publications must be prepared by the CI or delegate, and authorship agreed, where applicable, ensuring that US is credited as sponsor. A copy must be provided to the sponsor.

4.5.5 Dissemination of findings to participants must be agreed and actioned, as recommended by the Health Research Authority (HRA). Consideration should also be given to dissemination of the results to the study teams involved.

4.5.6 The TMF must be updated with all results, including the final report, statistical reports and publications, where applicable, prior to archiving.

4.5.7 The EuDRACT database must be updated with the details of the final report.

4.5.8 Once all actions are complete, a request to officially close the study must be sent to the Sponsorship Sub-Committee and approval to archive will be provided.

4.5.9 Archiving shall be carried out according to SOPRG33 - Archiving Paper Trial Documents (for University of Sussex as a Sponsor).

4.6 Early/ Premature Termination of a Study

4.6.1 A study may be terminated earlier than the planned closure date. Reasons for termination prior to the planned date include:

- Safety concerns
- Slow recruitment
- Poor toleration of the study intervention (patient related reaction)
- Sponsor's decision
- Investigator's decision
- Regulatory decision (e.g. MHRA)

4.6.2 In the case of termination earlier than the planned closure date indicated in the protocol, the REC must be notified within 15 days of the date of termination by submitting the Declaration of the End of Trial Form from the MHRA's webpages[2].

4.6.3 There must be clear documentation in the TMF about the decision to terminate a study early and communication to sites must be provided in an organised manner. This documentation must include a clear justification and rationale for the decision made by the appropriate personnel, which provides the evidence basis for the early termination.

4.6.4 Participants who are still active in the study must be notified of the study closure with reasons. A communication must be prepared by the CI or Trial Steering Committee with an agreed, unambiguous message to be disseminated by site staff. REC approval is not required but advice may be sought if the information provided is particularly sensitive or distressing.

4.6.5 Other standard procedures and processes for closing a study must be followed (sections 4.2 to 4.5 above)

2 http://ec.europa.eu/health/files/eudralex/vol-10/declaration_end_trial_form.doc
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safetyissues#end-of-trial

5. Training

This is a 'read and understand' SOP. Please note that the Research Ethics, Integrity and Governance Team discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the University website.

6. Abbreviations

AE	Adverse Event
BSMS	Brighton and Sussex Medical School
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF	Case report form
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DCF	Data Clarification Form
DSUR	Development Safety Update Report
eCRF	Electronic Case report form
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
HSC	Health and Social Care
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVD	In Vitro Diagnostic
JCRO	Joint Clinical Research Office
LIP	Local Information Pack
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator

PAF	Portfolio Application Form
PPI	Patient and Public Involvement
PVG	Pharmacovigilance Manager
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RM(ATIMPS)	Regulatory Manager for ATIMPS
RM(P)	Regulatory Manager (Pharmaceuticals)
SAE	Serious Adverse Event
SDV	Source Data Verification
SI	Statutory Instrument
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
TMF	Trial Master File
US	University of Sussex

7. Cross Referenced SOPs

SOPRG01a Sponsorship Approval of CTIMPs
SOPRG033 Archiving Paper Trial Documents for US as a Sponsor

8. References

Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, SI 1031
http://www.legislation.gov.uk/uksi/2004/1031/contents/made

ICH Good Clinical Practice
https://www.ich.org/page/efficacy-guidelines

Good Clinical Practice Guide MHRA/ Stationery Office (Great Britain), London: 2012

NIHR Clinical Trials Toolkit - http://www.ct-toolkit.ac.uk/