Hull University Teaching Hospitals NHS Trust

Department	Research & Development
Title of SOP	**End of Trial SOP**
SOP reference no.	R&D GCP SOP 12
Author	G Constable
Reviewed by	J Illingworth, S Moffat & L Cox
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Target audience	Research, pharmacy and R&D staff
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Signed copy kept in R&D Department

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This page details the version history and the main changes made for each new version.
The new changes are in red font.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 25.09.12	J Pacynko & J Illingworth	Original SOP approved by R&D Committee on 01.09.12
Version 2, 02.03.15	J Pacynko	Links checked and up-dated Mention of MHRA annual service fee removed. Mention of filing in the TMF of MHRA and REC acknowledgement correspondence for the end of trial form and trial report added.
Version 3, 06.05.16	S Moffat and J Pacynko	Explanation that the End of Trial Declaration form is now to be submitted via CESP. Addition of change of instructions regarding the end of trial summary report. The report now has to be uploaded to EudraCT by the Sponsor and a confirmation email sent to MHRA. Removal of reminders (6mth, 10mth and 12 mths) to be set up on Reda and replaced with reminders (6mth, 10mth and 12 mths) to be set up on Outlook. Updates to the process are in accordance with relevant HRA changes.
Version 4, 16.05.19	J Pacynko	4.9 R&D QA to be in control of randomization list, to make sure database lock occurs before release. 4.10 If statistical analysis is performed by the investigator, the trial statistician will need to check the analysis. 4.12 The results of the statistical analysis will need to be reviewed by the Sponsor and the review documented. 4.16 Publications will need to be reviewed on behalf of the Sponsor and this review documented in the Publication QC form (Working Instruction 13). 4.19 The Chief, Principal or Co-investigator (on behalf of the Sponsor) will need to upload the summary results to EudraCT **within 1 year** of the end of the trial. 4.20 Likewise if the trial has been registered with clinicaltrials.gov and/or ISRCTN, the CI/PI/Co-I will need to update these websites with the results of the trial **within 1 year** from the end of trial notification. 4.22 The format of the CSR should follow the guidelines in the ICH E3 document called 'Structure and content of Clinical Study Reports' 4.25 The Sponsor (R&D QA) is required to review the CSR and publications. The Sponsor review will be documented in the CSR QC form (WI 13) and saved in the TMF

Version 5, 03.01.23	G Constable & S Moffat	4.4 – Addition for submitting the EOT for trials not submitted through the Combined Review Process 4.5 – Addition for submitting the EOT for trials submitted through the Combined Review process 4.10 - Clarification of responsibilities 4.18 - Clarification of sending results to the R&D QA team 4.24 - Added notes on WI's used for end of trial procedures. 5.2 - Addition of Monday.com as an option to prompt investigators for the end of trial report. 5.5 - Added clarification/reiteration that the database should be locked prior to sending through to R&D QA. 5.7 - Clarification that archiving can be performed by any assessed third-party archivists and additional comments of WI's used.

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the HUTH R&D GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-huth-sponsored-ctimps/

1 Purpose

1.1 The purpose of this SOP is to describe the procedures to follow when a HUTH-sponsored CTIMP finishes.

1.2 Following these procedures will ensure compliance with the legal requirements stipulated in the UK clinical trial regulations (Medicines for Human Use Clinical Trials Regulations 2004 and subsequent amendments) and with ICH GCP (International Conference on Harmonisation Good Clinical Practice for clinical research).

2 Who should use this SOP

2.1 This SOP should be used by:

- All research staff involved with HUTH-sponsored CTIMPs – Chief/Principal Investigator, co-investigators, research nurses, clinical trial assistants, project managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HUTH R&D staff QA staff who manage the sponsorship of HUTH-sponsored CTIMPs.
- Research staff involved with clinical trials sponsored by an external organisation where the Sponsor has no SOP for the end of trial. HUTH R&D SOPs are defaulted to in this case.

3 When is the end of the trial?

3.1 The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment (see R&D GCP SOP 08 Amendments).

3.2 In most cases the end of trial will be the date of the last visit of the last patient in the trial.

3.3 The end of the recruitment period is not to be confused with the end of the trial. Recruitment finishes when the target number of patients has been reached. The trial should end when the last patient has had their final trial visit.

4 Investigator responsibilities

Informing the MHRA, REC/HRA and R&D of the end of trial

- **Timelines**

4.1 A 'Declaration of the end of a Clinical Trial' form (end of trial form) should be sent by the Chief/Principal Investigator to the MHRA and REC and R&D **within 90 days** of the trial conclusion - UK CT regulation 27 (1). The HRA does not need to be notified of the end of trial.

4.2 If a trial is terminated before the specified date for its conclusion then the CI/PI should notify the MHRA, REC and R&D **within 15 days** of the date of termination - UK CT regulation 27 (2).

- **End of trial form**

4.3 The R&D Monitor (or QA Manager) will remind investigators when the end of trial form is due and forward the form to investigators for completion.

4.4 For trials not submitted through the Combined Review process:

- The link to the form is in Working Instruction 23 in GCP SOPs & forms\Working instructions in ClinicalGov on the Y Drive.
- The CI/PI should complete and sign the form. If the trial has been terminated early, the form should include a brief explanation of the reasons for ending the trial.
- Email the form to the R&D Monitor (or QA Manager) to be checked before submission to the MHRA and REC.
- The R&D Monitor (or QA Manager) will submit the end of trial declaration using MHRA Submissions via the Human Medicines Tile. Please select 'Clinical Trial' as the Regulatory Activity and 'CT – EOT' from the Regulatory sub activity dropdown list.

4.5 For trials submitted through the Combined Review process:

- The end of trial form should be completed and submitted by the CI/PI in the new part of the Integrated Research Application System (IRAS). This automatically submits the notification to both the REC and MHRA.
- Before submission the completed form should be emailed to the R&D Monitor (or QA Manager) to be checked for completeness.

Data entry and dataset lock

4.7 Investigators should finish data entry and resolve any data queries. The final dataset should be 'locked' to ensure access is permanently restricted for final analysis. The procedures for data coding, entry and locking are detailed in the R&D GCP SOP 13 Data Management.

4.8 A copy of the 'locked' dataset must be sent to the R&D Manager (or Monitor/QA Manager) prior to statistical analysis.

4.9 For double-blind randomised trials where a 3rd party randomisation service holds the randomisation list, R&D QA will need to be in receipt of the complete set of trial data and

then request release of the randomisation list. R&D QA will then forward the list to the statistician and Chief/Principal Investigator and document the order of events on the Data Timelines Log (WI 19). The randomization service will be informed at the trial set-up phase that they can only release the list to the Sponsor when the trial has finished and that the request will come from the R&D QA staff.

Trial analysis

4.10 The CI, PI, Co-investigator or a delegated suitable Statistician will perform the statistical analysis. If the investigator performs the analysis, the trial statistician will need to check the analysis.

4.11 Any protocol deviations will need to be taken into account during the trial analysis.

4.12 The results of the statistical analysis will need to be reviewed by the Sponsor and this review documented. A suitably qualified colleague in HUTH or the University of Hull will be asked to review the analysis on behalf of the Sponsor and to sign off the Clinical Study Report (CSR) QC form (Working Instruction 13).

Publication and dissemination

4.13 The Chief, Principal or Co-investigator should write the publication or trial report.

4.14 Investigators are advised to check their response to question A53 of the IRAS form concerning informing participants of the results. Patients who have taken part in the trial should normally receive a summary of the trial findings in layman's terms unless the response to A53 states otherwise.

4.15 Randomised controlled trials (RCTs) should be reported in accordance with the CONSORT statement (Consolidated Standards of Reporting Trials http://www.consort-statement.org/). The CONSORT Statement is a minimum set of recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

4.16 Publications will need to be reviewed on behalf of the Sponsor and this review documented in the Publication QC form (Working Instruction 13).

End of trial summary report

- **Timelines and sending to MHRA, REC/HRA and R&D**

4.17 The Chief, Principal or Co-investigator must compile a summary of the final trial report **within 1 year** of the end of the trial.

4.18 The summary report should be emailed to the R&D QA team who will forward the report to the REC/HRA assistant. REC/HRA should acknowledge receipt of the report in an email which should be filed in the Trial Master File alongside the original signed end of trial form.

4.19 If a trial is registered with EudraCT and trial commences prior to January 2021 then the following (4.19.1) applies, Since January 2021, EudraCT is no longer a requirement. For new trials, the results should be published in the public register where the study is registered and the MHRA informed when this is done.

*4.19.1 The Chief, Principal or Co-investigator (on behalf of the Sponsor) will need to upload the summary results to EudraCT **within 1 year** of the end of the trial. The CI/PI/Co-I will then need to send an email confirming this has been done to the MHRA at CT.Submission@mhra.gsi.gov.uk with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' in the subject line and with R&D QA on copy. The MHRA will not send an acknowledgment email or letter. This is adhering to transparency regulations and is checked by the EMA.*

4.20 Likewise if the trial has been registered with clinicaltrials.gov and/or ISRCTN, the CI/PI/Co-I will need to update these websites with the results of the trial **within 1 year** from the end of trial notification.

- **Format of end of trial report**

4.21 The MHRA call the end of trial report the clinical study report (CSR).

4.22 The format of the CSR should follow the guidelines in the ICH E3 document called 'Structure and content of Clinical Study Reports'.

4.23 As a minimum (e.g. for single-site trials) the report should include:
- whether the trial has achieved its objectives,
- the main findings
- an analysis of all serious and non-serious adverse events.
- the feedback given to participants
- arrangements for the publication or dissemination of the research.

4.24 Working Instruction 49 End of Trial Procedures should be used in any event of closing, termination or halting of a trial for whatever reason. This form will guide the investigator through the necessary steps for implementing the halting of the trial with the timelines shown for each.

4.25 The Sponsor (R&D QA) is required to review the CSR and publications. The Sponsor review will be documented in the CSR QC form (WI 13) and saved in the TMF.

5 Sponsor responsibilities

5.1 When informed by the CI/PI that the trial has ended, the R&D Monitor (or QA Manager) will forward the end of trial form to the CI/PI and remind him/her of the timelines for submission.

5.2 The R&D Monitor will set up reminders (6mth, 10mth and 12 mths) on the R&D QA Microsoft Outlook Calendar or Monday.com (for example) so that the Chief/Principal Investigator will be alerted well before the final trial report is due.

5.3 The R&D Monitor (or QA Manager) or CI/PI (depending if the trial was or was not submitted via the Combined Review process) will submit the end of trial form to the MHRA and REC and submit the summary trial report to the REC.

5.4 Upon receipt of the signed end of trial form at R&D, the R&D monitor (or QA Manager) will scan and email a copy to pharmacy clinical trials. A copy of the end of trial form will be filed in the Trial Master File or Sponsor Study File and a copy in the R&D office folder. An electronic copy will be saved in the Sponsor's electronic Trial Master File or Sponsor Study File.

5.5 For double-blind randomised trials where the randomisation list is held by a 3rd party, R&D QA will need to be in receipt of the complete and locked set of trial data before they request the

release of the randomisation list to R&D QA from the randomisation service. R&D QA need to control the release of the randomisation list (on behalf of the Sponsor) so that this occurs after the database is locked and the timings are documented on the Data Timelines Log (WI 19).

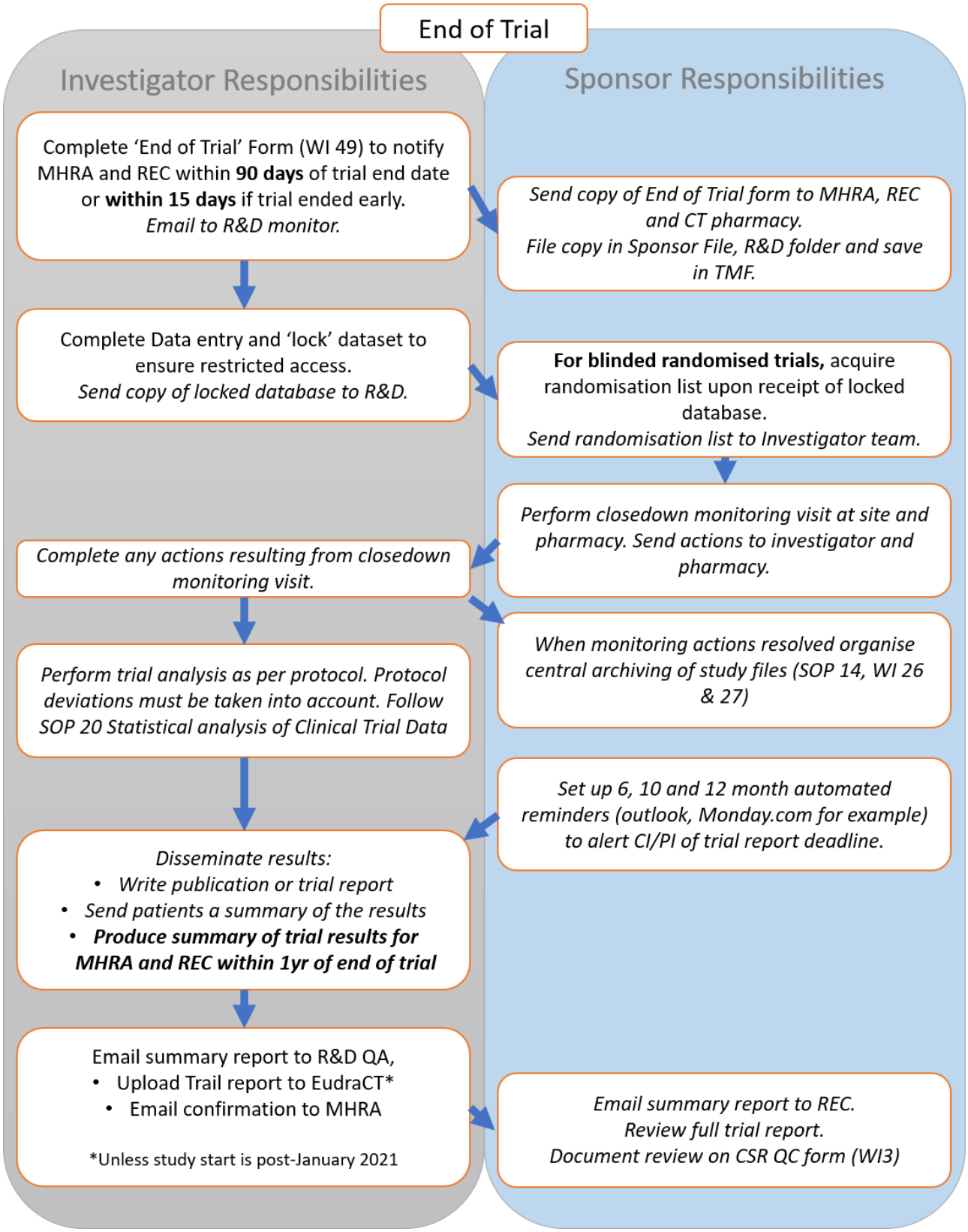
5.6 The R&D Monitor will perform a closedown-monitoring visit at site, pharmacy and laboratory (if applicable) to check the Trial Master File, the CRFs, patients' medical records, Pharmacy Study File and Laboratory Study File.

5.7 When actions from the closedown visit have been resolved by investigators, then the monitor will organize the central archiving of the Trial Master File, CRFs, Sponsor Study File and Pharmacy Study File according to the R&D GCP SOP 14 Archiving (utilizing WI 26 Receipt of files for archiving and WI 27 Archive box contents and permissions form). Study files to be archived should be sent to an assessed third party archivist such as the Restore Archive Storage Facility.

6 Implementation

6.1 Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

Appendix 1


End of Trial
Investigator Responsibilities
Sponsor Responsibilities
Complete 'End of Trial' Form (WI 49) to notify MHRA and REC within **90 days** of trial end date or **within 15 days** if trial ended early.
Email to R&D monitor.
Send copy of End of Trial form to MHRA, REC and CT pharmacy.
File copy in Sponsor File, R&D folder and save in TMF.
Complete Data entry and 'lock' dataset to ensure restricted access.
Send copy of locked database to R&D.
For blinded randomised trials, acquire randomisation list upon receipt of locked database.
Send randomisation list to Investigator team.
Perform closedown monitoring visit at site and pharmacy. Send actions to investigator and pharmacy.
Complete any actions resulting from closedown monitoring visit.
When monitoring actions resolved organise central archiving of study files (SOP 14, WI 26 & 27)
Perform trial analysis as per protocol. Protocol deviations must be taken into account. Follow SOP 20 Statistical analysis of Clinical Trial Data
Set up 6, 10 and 12 month automated reminders (outlook, Monday.com for example) to alert CI/PI of trial report deadline.
Disseminate results:
• *Write publication or trial report*
• *Send patients a summary of the results*
• ***Produce summary of trial results for MHRA and REC within 1yr of end of trial***
Email summary report to R&D QA,
• Upload Trail report to EudraCT*
• Email confirmation to MHRA
*Unless study start is post-January 2021
Email summary report to REC.
Review full trial report.
Document review on CSR QC form (WI3)