Standard Operating Procedure For Investigators and Sponsor for End of Trial Notification Procedures

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Revision Chronology:			
Version Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JBRU/INV/S07/01	14/01/10	To implement formatting changes to comply with the SOP on SOPs (JRO/SPON/S01/02). To bring the content up to date with the sponsor's procedures for the Declaration of the End of Trial Notification Form, close out and trial reporting requirements.	Anne Marie Downey and Ann Cochrane
JRO/INV/S07/02	14/10/11	To further clarify the responsibilities of the Investigators and Sponsor for End of Trial Notification, Trial Close Out Procedures and to add the request of the final statistical plan.	Anne Marie Downey and Nimrita Verma
JRO/INV/S07/03	08/08/14	Updated end of trial procedure for single site and multi-centre trials and clarified on-site and central close out monitoring procedure	Harshani Hettiarachchi Gemma Jones
JRO/INV/S07/04	08/08/17	Updated information on EudraCT reporting	Adedayo Akinyemi
JRO/SPON/S06/01	30/11/20	Revised all sections of the SOP document. Removed close out procedures (added to a separate SOP document). Added section 6.4 Preparation for Archiving	Samim Patel / Catherine Maidens
JRO/SPON/S06/02	30/11/23	Added HRA guidelines for retained tissue at end of trial. Added process for HRA combined review trials. Added HRA Lay Summary process. Added process for reporting of results on public registers and CTIS	Samim Patel / Catherine Maidens

ACRONYMS:	
ATIMP	Advanced Therapy Investigational Medicinal Product
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
ISF	Investigator Site File
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
IMP	Investigational Medicinal Product
JRO	Joint Research Office (representative of the Sponsor) https://www.ucl.ac.uk/joint-research-office/
PI	Principal Investigator
PVG	Pharmacovigilance
RM (ATIMP)	Regulatory Manager (Advanced Therapy Investigational Medicinal Product)
RM (P)	Regulatory Manager (Pharmaceuticals)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Statutory Instrument
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
TMF	Trial Master File

Standard Operating Procedure for Sponsor and Investigators for End of Trial Notification Procedures

1. PURPOSE

This Standard Operating Procedure (SOP) has been written to describe the procedures for Investigators and Sponsor for the end of trial notification procedures and reporting requirements.

2. JOINT UCLH/UCL RESEARCH OFFICE (JRO) POLICY

All SOPs produced from the JRO must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

All JRO SOPs will be produced, reviewed and approved in accordance with the JRO SOP on SOPs.

Please refer to the JRO website to ensure that this is the most current version of the SOP.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, as UCL sponsors trials with EU and Northern Ireland sites, the SOPs are written to comply with EU Clinical Trials Regulation No. 536/2014.

The Medicines for Human Use (Clinical Trials) Regulations SI 2004/1031 as amended outline the responsibilities of the Sponsor to notify the REC and Competent Authority (MHRA in UK) after the conclusion of a trial (UK Regulation No. 27). End of trial monitoring procedures should be in place to ensure data quality and accurate reporting of trial data for the end of trial report and final trial analysis, and to ensure that essential documents in the Trial Master Files/Investigator Site Files are complete and ready for archiving as per Sponsor SOP 21.

4. SCOPE OF THIS SOP

This SOP will describe the process for Investigators and the Sponsor to follow at the conclusion of a trial, publication of results and their responsibilities to inform the Competent Authority and REC.

This SOP refers to CTIMPs sponsored by UCL and managed by the JRO. This SOP will not apply to trials that are managed by a third party; where they have contractually been delegated end of trial notification and close out procedures in line with their SOPs.

5. RESPONSIBLE PERSONNEL

Responsibilities of Personnel are outlined in the tables found in section 6.

6. PROCEDURE

6.1 Notification of End of Trial

The definition of the end of the trial should be documented in the protocol.

For most clinical trials this will be the date of the last visit of the last participant. It may also be the completion of any follow-up monitoring and data collection, as described in the protocol. For international studies, this is the end of trial in all participating countries, not just in the UK.

For studies involving human tissue, the analysis of the samples should be undertaken as part of the data collection before the end of trial is declared.

Any retained tissue for possible future evaluation after the end of trial has been declared, should be with the appropriate licence and should be undertaken as described in the protocol and within the terms of consent from the donors. Otherwise, a new proposal for REC review would need to be submitted.

Any change to the end of study definition after approval has been given for the research should be notified as an amendment to the appropriate review bodies.

	Responsible Person	Activity
1	CI / Delegate	Notify Sponsor of the Trial End Date as defined in the trial protocol or if the trial has prematurely ended (early termination).
2	SRA / RM (ATIMP)	Confirm with CI that all trial activities as per the protocol have been completed. Confirm with CI and study team that the plans that were approved by the REC for use of tissue and data collected in the course of the study, providing information to participants, and dissemination of results remain unchanged. Confirm that all study specific sample analysis has been completed, and/or any changes to other trial documents have been undertaken via an amendment prior to notification. NB: No study amendments can be undertaken once the end of trial form has been submitted.
3	SRA / RM (ATIMP)	Confirm with Trial Statistician / CI if there are any major changes to the initial Statistical Analysis Plan detailed in the Protocol. These include changes to primary outcome or its definition, added outcomes or new subgroup analyses. Confirm with Trial Statistician if a separate Statistical Analysis Plan (SAP) document will be produced and request a copy for filing in the Sponsor File.

	Responsible Person	Activity
		Check that the SAP document has been reviewed and approved by the CI. Check with the Statistician that the SAP has been produced in line with the current approved protocol version. If there is no separate SAP document, confirm with the Trial Statistician that the analysis will be undertaken in line with the Statistics and Data Analysis section of the current approved version of the protocol. File confirmation in the Sponsor File. Note: If changes are required to the analysis section of the protocol, the amendment must be submitted and approved prior to the End of Trial notification.
4	SRA / RM (ATIMP)	Complete the **Declaration of the End of Trial Form** and submit to REC & MHRA within the notification timelines: • Within 90 days for a planned conclusion of a Trial. • Within 15 days for a premature conclusion of a Trial (early termination). For trials that <u>were not</u> submitted through combined review: • Email the completed form to REC copying in the CI. • Submit to MHRA along with a Cover Letter (associated template **MHRA EoT Cover Letter Template**) via the MHRA Submissions website (select Human Medicines Tile, then 'Clinical Trial' as the Regulatory Activity and 'CT – EOT' from the Regulatory sub activity dropdown list). For trials that were submitted through Combined Review: • Complete and submit the End of Trial Form found on the 'Reporting' tab. • Print a PDF of the completed form for filing.
5	SRA / RM (ATIMP)	File all documents (completed form and REC / MHRA acknowledgments) in the Sponsor File. Send all documents (completed form and REC / MHRA acknowledgments) to the CI / Delegate for filing in the TMF. Update the status on EDGE. Inform CI / Delegate to update CPMS if applicable (CPMS only applies to NIHR Portfolio adopted trials).
6	SRA / RM (ATIMP)	Inform the PVG Manager and COA/Trial Monitor of the End of Trial.
7	COA /Trial Monitor	Monitoring Close Out procedure initiated as per Section 6.2 of the SOP (JRO/SPON/SOP10) and the Trial Monitoring Plan.
8	CI / Delegate / SRA / RM (ATIMP)	Notify contracted parties (as per signed agreement) (e.g. sites, funder, central laboratories, IMP supplier, database provider) of the end of the trial once all relevant activities are completed.

6.2 End of Trial Results

Clinical trial summary results must be published within **one year of the end of trial** in the public register(s) where the clinical trial has been registered.

The trial data analysis needs to be undertaken in accordance with the Statistical Analysis Plan (SAP) as soon as possible after the end of trial declaration. The analysis should only be done once all trial data has been collected, cleaned, checked, data queries resolved, and the trial database has been locked.

A lay summary report should be produced for uploading onto the IRAS Combined Review system or HRA website (for studies not submitted via Combined Review). Refer to the guidance on how to write lay summaries on the HRA website.

For the public registries, ensure the analysis includes results data in the format specified by the registry.

6.3 End of Trial Report Submission

The regulatory time frame for publishing the summary of results is within one year of the end of trial date. In the case of a delay, the MHRA and REC must be notified as soon as possible explaining the reason for the report delay and future submission date.

The summary results should be published on:
- IRAS Combined Review system or HRA website (for studies not submitted via Combined Review).
- All public registries where the trial has been registered.

6.3.1 REC/HRA Lay Summary <u>via IRAS Combined Review</u>

	Responsible Person	Activity
1	CI / Delegate	Complete the Final Report form under the 'Reporting' tab and save. (NB: <u>Do not</u> submit at this stage). Print to PDF and send to the SRA / RM (ATIMP).
2	SRA / RM (ATIMP)	Review to check trial information has been completed correctly (e.g., recruitment figures). Send the PDF to PVG Manager for review of adverse events information. Send the PDF to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Statistician approval email in the Sponsor File.

	Responsible Person	Activity
		Inform CI / Delegate to submit completed report on the IRAS Combined Review system.
3	CI / Delegate	Inform SRA / RM (ATIMP) when the Final Report form has been submitted and send PDF copy of the submitted form. File PDF copy of submitted Final Report Form in the TMF.
4	SRA / RM (ATIMP)	File copy of submitted Final Report Form in the Sponsor File.

6.3.2 REC/HRA Lay Summary via HRA Website (trials not approved via Combined Review)

	Responsible Person	Activity
1	CI / Delegate	Send lay summary report to SRA / RM (ATIMP).
2	SRA / RM (ATIMP)	Review to check trial information has been completed correctly (e.g. recruitment figures). Send the lay summary report to PVG Manager for review of adverse events information. Send the lay summary report to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Trial Statistician approval email in the Sponsor File. Inform CI / Delegate to complete the Webform on the HRA website and submit.
3	CI / Delegate	Inform SRA / RM (ATIMP) when the Webform has been submitted and send PDF copy of the submitted form. File PDF copy of submitted Form in the TMF.
4	SRA / RM (ATIMP)	File copy of submitted Webform in the Sponsor File.

6.3.3 Results Reporting on Public Registries

When results have been published on a public registry, email the MHRA on CT.Submission@mhra.gov.uk to inform them.

The subject line of the email notification must state ‘End of trial: result-related information: EudraCT XXXX-XXXXXX-XX’ and/or IRAS ID XXXXXXX’.

File the email notification in the Sponsor File.

6.3.3.1 ISRCTN

	Responsible Person	Activity
1	CI / Delegate	Ensure all trial information is up to date and prepare results summary as per the guidance on the ISRCTN website. Send results summary report to SRA / RM (ATIMP).
2	SRA / RM (ATIMP)	Review to check trial information has been completed correctly (e.g. recruitment figures). Send results summary report to PVG Manager for review of adverse events information. Send the results summary report to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Statistician approval email in the Sponsor File. Inform CI / Delegate to upload results summary onto the ISRCTN website.
3	CI / Delegate	Inform SRA / RM (ATIMP) when the results have been uploaded and send copy of the final uploaded results. File copy of uploaded results in the TMF.
4	SRA / RM (ATIMP)	File copy of uploaded results in the Sponsor File.

6.3.3.2 ClinicalTrials.gov

	Responsible Person	Activity
1	CI / Delegate	Ensure all trial information is up to date and complete the results section. Download PDF and send to the SRA / RM (ATIMP) when completed.
2	SRA / RM (ATIMP)	Review to check trial information has been completed correctly (e.g. recruitment figures). Send the PDF to PVG Manager for review of adverse events information. Send the PDF to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Statistician approval email in the Sponsor File.

	Responsible Person	Activity
		Inform CI / Delegate to submit the record on the system for release to Clinicaltrials.gov.
3	CI / Delegate	Inform SRA / RM (ATIMP) when the record has been published on the system and send PDF copy of the record. File copy of published results in the TMF.
4	SRA / RM (ATIMP)	File copy of published results in the Sponsor File.

6.3.3.3 EudraCT

For trials that are registered in the public area of the European Clinical Trials Database (EudraCT), the results need to be completed following the pre-determined dataset on the system. Note: the MHRA will not be able to update the status of the trial in the EU system.

	Responsible Person	Activity
1	SRA/ RM (ATMP)	Refer to the **Submission of Clinical Trial Results in EudraCT- Sponsor Guide** document. Send CI / Delegate the **Submission of Clinical Trial Results in EudraCT – Investigator Guide** document and instruct them to begin the process as per the guide.
2	CI / Delegate	CI / Delegate must follow the **Submission of Clinical Trial Results in EudraCT - Investigator Guide** to ensure study information is captured in the pre-determined dataset, validated and uploaded in EudraCT. Inform SRA / RM (ATIMP) when the draft results have been uploaded.
3	SRA/ RM (ATMP)	Review to check trial information has been completed correctly (e.g., recruitment figures, sponsor information). Send the PDF to PVG Manager for review of adverse events information. Send the PDF to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Statistician approval email in the Sponsor File. The SRA/RM will post results in EudraCT, download a pdf of the final results for filing in the Sponsor File, and send a copy to the CI / Delegate for filing in the TMF.

6.3.3.4 Clinical Trials with EU sites registered on Clinical Trial Information System (CTIS)

A summary of results, accompanied by a lay person summary of results, must be uploaded onto CTIS within 12 months of the end of trial. The summary of results must follow the content outlined in Annex IV of the EU Clinical Trials Regulation No. 536/2014, and the lay summary must follow the content outlined in Annex IV of the EU Clinical Trials Regulation No. 536/2014.

	Responsible Person	Activity
1	CI / Delegate	Send summary of results and lay person summary of results reports to SRA / RM (ATIMP).
2	SRA / RM (ATIMP)	Review to check trial information has been completed correctly (e.g., recruitment figures). Send the reports to the PVG Manager for review of adverse events information. Send the reports to the Trial Statistician for review and to confirm that the results are accurate and consistent with the final analysis. Inform CI / Delegate of any corrections to be made if applicable. File the Statistician approval email in the Sponsor File. Inform CI / Delegate to submit the summary of results and lay person summary of results.
3	CI / Delegate	Select the 'Trial results' tab within CTIS and upload the summary of results and lay person summary of results reports. Inform SRA / RM (ATIMP) when the reports have been submitted on the system and send copies of the reports. File copy of submitted reports in the TMF.
4	SRA / RM (ATIMP)	File copy of submitted reports in the Sponsor File.

6.4 Preparation for Archiving

Preparation for archiving of the trial documents can begin after the End of Trial Results have been reported. Prior to archiving a full review of the TMF and Sponsor File should be carried out to ensure all documents are filed and any missing documents are file noted.

	Responsible Person	Activity

1	CI	Perform a full review of the TMF. Any missing documents should be filed or a file noted. When the Sponsor has issued the Archiving Confirmation email, proceed to archiving the TMF as per the Sponsor's SOP on Archiving (SOP 21).
2	SRA / RM (ATMP)	Perform a full review of the Sponsor File. Any missing documents should be filed, or file noted. Archive the Sponsor File as per the Archiving SOP (SOP 21).

7. REFERENCES

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031, implemented 1st May 2004, and as amended thereafter.

2. EU Clinical Trials Regulation No. 536/2014

3. European Comission: Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), March 2010

4. Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

5. Sponsor's SOP on Archiving

8. APPENDICES

No Appendices are associated with this SOP.

9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP

1.	MHRA End of Trial Cover Letter Template
2.	Submission of Clinical Trial Results in EudraCT - Sponsor Guide
3.	Submission of Clinical Trial Results in EudraCT - Investigator Guide

10. SOP DISSEMINATION & TRAINING

This SOP will be available to the CIs on https://www.ucl.ac.uk/joint-research-office/
Trial team staff concerned by this SOP will sign the SOP training log (12. SOP TRAINING LOG) part of this SOP.

This SOP will be distributed to the concerned JRO staff. Staff concerned by the SOP will sign the SOP training log (12. SOP TRAINING LOG) which is part of each SOP.

The training will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP.

11. SIGNATURE PAGE

Author and Job Title:	Samim Patel, Sponsor Regulatory Advisor
Signature:	DocuSigned by: Samim Patel E218F1144A624FA...
Date:	30 October 2023 | 11:40 GMT

Authorised by: **Name and Job Title**	Helen Cadiou, Head of Quality Assurance
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	30 October 2023 | 11:46 GMT

12. SOP TRAINING LOG:

	Name of Staff (Capital letters)	**Job Title: Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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