Standard Operating Procedure for the Classification, Review and Submission of Clinical Trial Amendments

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Revision Chronology:			
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JBRU/07/S09/00	26/11/07	N/A	Ira Jakupovic
JBRU/INV/S03/01	03/07/08	To make SOP specific to Investigator responsibilities. To implement new JBRU formatting and numbering system as reflected in SOP on SOPs (JBRU/SPON/S01/02).	Ira Jakupovic
JBRU/SPON/S13/02	10/01/10	To combine: 1. the sponsor ”SOP for the Sponsor’s Management of Clinical Trials Amendments and Urgent Safety measures” (SPON/S13/01) and 2. the investigator “SOP for 1. Classification, review and submission of Clinical Trials Amendments 2. Urgent Safety measures” (INV/S03/S01) on amendments, To slightly modify as per current JBRU procedure. Format amended in line with revised SOP on SOPs to incorporate a UCL logo only, as UCLH no longer provides sponsorship for CTIMPs, an Acronyms table, eDocument file path, associated templates/log table, SOP dissemination and training and a signature page.	Alison Evans
JBRU/SPON/S13/03	18/05/11	SOP update to reflect updated regulatory procedures for processing Amendments and make the SOP specific to JBRU responsibilities.	Nimrita Verma
JRO/SPON/S13/04	18/05/14	Addition of Amendment Review Form	Adedayo Akinyemi
JRO/SPON/S13/05	01/06/15	SOP update to reflect the new NHS/HSC R&D submission and approval procedure for amendments	Michelle Quaye
JRO/SPON/S13/06	22/07/16	Commissioning of the HRA principles	Shriram Velamuri
JRO/SPON/S13/07	27/07/19	Updates to process for non-substantial amendments from CI responsibility to JRO responsibility. Addition of process diagram for submission process and links to guidance from HRA, IRAS and MHRA. Information on amendments involving updates to Reference Safety Information or quality data of Investigational Medicinal Product.	Catherine Maidens
JRO/SPON/S13/08	20/11/21	Update to reflect new regulatory process for the review and categorisation of amendments.	Nikkayla Dixon
JRO/SPON/S13/09	08/06/24	Updates to reflect the new process for trials approved via IRAS Combined Review.	Catherine Maidens / Samim Patel

ACRONYMS:	
CI	Chief Investigator
CRO	Contract Research Organisation
CTIMPS	Clinical Trials of Investigational Medicinal Products
CTOM	Clinical Trials Operations Manager
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
HSC	Health and Social Care in Northern Ireland
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File
JRO	Joint Research Office
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research and Development
NIHR	National Institute for Health Research
PI	Principal Investigator
PIC	Participant Identification Centres
PV	Pharmacovigilance
REC	Research Ethics Committee
RM (ATMP)	Regulatory Manager for Advanced Therapy
RMP	Regulatory Manager for Pharmaceuticals
RSI	Reference Safety Information
SI	Statutory Instrument
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
TMF	Trial Master File
UCL	University College London

SOP for the Classification, Review and Submission of Clinical Trial Amendments

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for the Sponsor to review and submit amendments of Clinical Trials of Investigational Medicinal Products (CTIMPs).

2. JOINT RESEARCH OFFICE POLICY

All Joint Research Office (JRO) SOPs will be produced, reviewed and approved in accordance with the JRO SOP on SOPs.

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.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in 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 Trial Regulation 536/2014 (CTR).

Amendments are changes made to a clinical trial, after a favourable ethical opinion and/or approval by a regulatory body has been given. Amendments can be made to any information relating to a trial or an approved protocol.

If an amendment is required, it must be determined which of the review body(ies) from whom initial approvals were received need to give approval of the amendment. Different review bodies have different requirements.

An amendment to a clinical trial can be either **substantial** or **non-substantial** in nature. The Sponsor must be notified of all amendments.

Roles and Responsibilities for submitting amendments will be agreed at the beginning of the trial with the Investigator, Sponsor and (if applicable) named delegate such as a CTU, CRO or specialist consultancy in form of a contractual agreement.

3.1.1 Substantial Amendments

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as **'substantial'** when they have a significant impact on:

- The safety or physical or mental integrity of the clinical participants; or,

- The scientific value of the trial; or
- The conduct or management of the study; or
- The quality or safety of any Investigational Medicinal Product (IMP) used in the trial.

3.1.2 Non-substantial Amendments

Amendments not classed as substantial, are defined as 'non-substantial' amendments.

Further information on the classification of amendments can be obtained from the **European Commission CT1 2010/C 82/01** document and from the HRA website: https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/

4. SCOPE OF THIS SOP

This SOP details the process for reviewing, classifying and, if applicable, submitting amendments for Joint Research Office (JRO) managed UCL sponsored clinical trials.

The JRO is the representative of the Sponsor. The Sponsor will be referred to as JRO in this SOP.

When an external Clinical Trials Unit (CTU) / Contract Research Organisation (CRO) has been appointed by the JRO to perform the trial management activities on behalf of the Sponsor; this SOP will be used in conjunction with the relevant CTU/CRO SOP.

5. RESPONSIBLE PERSONNEL

Responsibilities are outlined in section 6.

6. PROCEDURES

6.1 Receipt of Amendment from Chief Investigator or delegate

Responsible Person	Task
Chief Investigator (CI) / contractually agreed delegate	Notifies JRO that amendments to trial documentation are required.
CI / contractually agreed delegate	Provides JRO with the completed **Amendment Tool** from the IRAS website, and any trial associated documents that have been modified (e.g., Patient Information Sheet (PIS), Consent Form, Protocol, Investigational Medicinal Product Dossier (IMPD) etc.). All modified documents should be in a tracked-changes format to show previous and new wording, and must be version controlled (i.e., version number and date updated).

6.2 Review and Classification of Amendments

Responsible Person	Task
Sponsor Regulatory Advisor (SRA) / Regulatory Manager – Advanced Therapies (RM (ATMP)	**Initial review of amendment:** The updated documents are reviewed by the JRO, and details of the updates are added to the **HRA Amendment Tool** (refer to the IRAS website for the latest version of the Amendment Tool) to confirm if the amendment is **substantial** or **non-substantial**. Note 1: Certain amendments need to be submitted separately. **For trials approved via IRAS Combined Review** the following amendment types cannot be combined with any other changes: • **Substantial: Chief Investigator** (for amendments to change the CI) • **Substantial: Sponsor Group** (for amendments to change the sponsor or sponsor's legal rep) • **Substantial: Administrative** (if you are only changing the contact details for the CI, sponsor, sponsor contact or sponsor legal rep) • **Non-substantial: Extend Study End Date** In addition, 'Chief Investigator', 'Sponsor Group' and 'Administrative' amendments can only be made one at a time. It is however possible to have more than one 'Project Information' amendment in progress at a time. Note 2: Addition of a **new site** or change of **Principal Investigator** should **not** be grouped with other amendments but submitted separately to expedite the site set-up process.
SRA / RM(ATMP) / Regulatory Manager for Pharmaceuticals (RMP) / Pharmacovigilance (PV) Manager	**Additional considerations when amendment includes IMP documentation updates:** Where the amendment includes an update to the **Reference Safety Information (RSI)** for the trial (contained within an Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)), it must be classified as a **substantial amendment**. A tracked-changes version of the IB/SmPC should be provided so differences can be easily viewed. Consult PV Manager. Where the amendment has been classified as substantial and does not already include an update to the RSI, check with the PV manager if there have been any updates to the SmPC/IB containing the RSI. Include any RSI update with the amendment as applicable. As listed in section 3.1.1 amendments relating to **IMP quality data** can be considered as substantial and may require subsequent changes to the Investigational Medicinal Product Dossier (IMPD) if these changes have not already been covered in the submitted IMPD. Consult RMP Manager. European Medicines Agency guidelines on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials can be sought for further guidance: https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-and-pharmaceutical-quality-documentation-concerning-investigational-medicinal-products-clinical-trials-revision-2_en.pdf (section 9)

SRA / RM (ATMP) / and/or JRO team members	**Categorisation using Amendment Tool:** The Amendment Tool will categorise amendments by an Overall Amendment Type and an Overall Category as below: <u>Overall Amendment Type:</u> - Substantial For Review - Substantial For Information - Substantial New Site / PI Only - Non-Substantial - Non-Substantial, No Study Wide Review Required - Non-notifiable <u>Overall Category:</u> • **Category A** – meaning the amendment has implications for or affects <u>all</u> participating NHS organisations. This may involve changes to activity or cost implications for the organisation. • **Category B** – meaning the amendment has implications for or affects specific participating NHS organisations. This may involve changes to activity or cost implications for these organisations. • **Category C** – meaning the amendment has no implications that require management or oversight by the participating organisations. The amendment is still provided for information but there are no changes to site activity or cost implications. Participating organisations might need to take some action, such as updating contact details. • **Category New site** – Amendment to a research study that only those participating NHS organisations affected by the amendment are expected to consider. • **Category N/A** – Amendment to a research study that is considered non-notifiable and NHS organisations are not expected to consider.
SRA / RM (ATMP)	Complete the **Amendment Review Form** (*associated template*) documenting the final decision of **substantial** or **non-substantial amendment**.
SRA / RM (ATMP) / PV Manager	The **Amendment Cover Letter** is drafted using the associated template. The cover letter should list all the updated documents included (tracked and clean versions) and summarise the reasons for the amendment / updates to the documents. For amendments including an updated IB/SmPC, the cover letter must indicate if the RSI is being updated. If an update to the RSI is not accompanied by a protocol amendment, the cover letter must state the risk mitigation measures already in place in the protocol to manage any new safety issues and if these new safety issues are adequately covered in the patient information sheet or if it needs to be updated. References to any parallel Development Safety Update Report (DSUR) submission should also be given in the cover letter. Consult PV Manager. The cover letter should also include details of any previous non-substantial amendments as applicable. Amendments submitted to MHRA require payment. Request Purchase Order (PO) to be raised by the CI / Trial Manager. The cover letter should clearly highlight the Purchase Order (PO) number.

SRA / RM (ATMP), and/or JRO team members	Consider whether any updates to the **Full Risk Assessment** are needed due to the updates made in the amendment (e.g., updates to safety information regarding the Investigational Medicinal Product (IMP), addition of new trial procedures, additional sites etc.). Any updates to the full risk assessment should be presented and discussed at the Clinical Operations Meeting.
SRA / RM (ATMP) / JRO team members	A separate review of the full amendment pack (i.e., completed Amendment Tool, updated documents, cover letter and Amendment Review Form) must be performed by a member of the CTIMPs team who will counter-sign the **Amendment Review Form** as reviewer. *Note:* Where the trial is managed by an external CTU/CRO who have prepared the amendment, the SRA / RM (ATMP) reviews the amendment pack as above and completes the Amendment Review Form. The completed Amendment Review Form and amendment pack is then reviewed by another member of the CTIMPs team who will counter-sign the Amendment Review Form as reviewer.
SRA / RM (ATMP) or contractually agreed delegate	Once the reviews are complete the **Amendment Tool** can be 'locked for submission'.
SRA / RM (ATMP)	File the amendment pack, locked amendment tool and relevant correspondence of amendment review by JRO / CI / Trial team and the signed Amendment Review Form in the JRO Sponsor File.

6.3 Submission of Amendments

Responsible Person	Task
SRA / RM (ATMP) / contractually agreed delegate	**For trials <u>not approved</u> via IRAS Combined Review:** Following review and approval, the SRA / RM (ATMP) / contractually agreed delegate submits the amendment as described on the following websites: HRA: https://www.hra.nhs.uk/approvals-amendments/amending-approval/ IRAS: https://www.myresearchproject.org.uk/help/hlpamendments.aspx https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx MHRA: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues <u>Note:</u> Substantial amendments that **only the MHRA** assesses (e.g., Investigational Medicinal Product (IMP) quality data) should be submitted just to the MHRA. The REC should be notified for information only in the next substantial amendment to the REC. Substantial amendments that **only the REC** assesses (e.g., facilities for the trial) should be submitted just to the REC. The MHRA should be notified for information only in the next substantial amendment to the MHRA.

	Save the submission confirmation / acknowledgment email in the Sponsor File.
SRA / RM (ATMP) / CI / contractually agreed delegate	**For trials approved via IRAS Combined Review:** Following review and approval, the SRA / RM (ATMP) / contractually agreed delegate submits the amendment as per the HRA guidance described on the following link: https://myresearchproject.org.uk/crirasguide/amendments.html Save the submission confirmation / acknowledgment email in the Sponsor File.
SRA / RM (ATMP) / CI / contractually agreed delegate	Update the **Amendment Log** *(associated template)* for the trial. CI / Contractually agreed delegate files all submission documents in the TMF and sends copies to the Sponsor. Or SRA / RM (ATMP) files copies of all submission documents in the JRO Sponsor File and provides copies to the CI / Delegate to file in the TMF.

6.4 Receipt of Approval, Implementation and Dissemination of Information

Responsible Person	**Task**
SRA / RM (ATMP) / contractually agreed delegate	Amendments **must not** be implemented until all applicable approvals are in place. Following receipt of the HRA validation/approval email / MHRA approval letter / REC approval letter as applicable, the SRA / RM (ATMP) / contractually agreed delegate notifies participating sites (NHS R&D and trial teams) and LCRN (if applicable). Refer to the example **Notification Email Template** *(associated template)* or the Notification Email Templates on the HRA website: https://www.hra.nhs.uk/approvals-amendments/amending-approval/ If the amendment has been determined by the Amendment Tool to be **Category A** or **B**, participating sites have 35 days to raise any objections, after which if no objections have been raised, the amendment can be implemented. **Category C** and **Category New Site** amendments can be implemented immediately. It is optional for NHS R&D offices to issue a continuing permission document / amendment acknowledgment; therefore one may not be received. If a continuing permission document / amendment acknowledgment has been received, this must be filed in the TMF, ISF and the JRO sponsor file.
SRA / RM (ATMP) / CI / contractually agreed delegate	For NIHR portfolio adopted trials, details may need to be updated on the CPMS system if the amendment affects for example, the recruitment target, trial start date or end date. If applicable, email the CI/Trial Manager/contractually agreed delegate to update the details on the CPMS system. If assistance required, contact the LCRN (North Thames).

SRA / RM (ATMP)	Update the Amendment Log with approval dates. File all approval letters in JRO Sponsor File. Ensure all updated approved documents are filed in the appropriate folder in the Sponsor File and previous versions moved to the superseded folder.
CI / contractually agreed delegate	File all approval letters in the TMF. Ensure all updated approved documents are filed in the appropriate folder in the TMF and previous versions moved to the superseded section.
SRA / RM (ATMP) / contractually agreed delegate	Once R&D acknowledgement / approval received or 35 days have elapsed, send the amendment package to the study team at the study site(s), including all applicable departments/contractors (e.g., Pharmacy, Labs, manufacturers). Instruct site(s)/parties to supersede the previous documents in the relevant file (e.g., ISF, lab file) and use the new updated versions. File email sent to site in the Sponsor File / TMF and update the Amendment Log with the amendment implementation date at site.

7. REFERENCES

1. European Commission CT1 (2010/C 82/01)

2. http://www.hra.nhs.uk/

3. https://www.myresearchproject.org.uk/help/hlpamendments.aspx

4. https://myresearchproject.org.uk/crirasguide/amendments.html

5. https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

6. https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal

8. APPENDICES

N/A

9. TEMPLATES/LOGS/SOPs ASSOCIATED TO THIS SOP:

1	Amendment Log Template
2	Amendment Review Form
3	JRO Amendment Cover Letter Template
4	R&D Amendment Email Template

10. SOP DISSEMINATION & TRAINING

SOPs relevant to the JRO only, will be distributed to the concerned JRO staff. Staff involved by the SOP will sign the SOP training log (Section 12. SOP TRAINING LOG) which is part of each SOP.

The training will constitute of the person reading the SOP and asking specific questions to the author of the SOP.

SOPs relevant to JRO staff and investigators or investigators only will be provided to the investigators during trial set-up where applicable and at the time of the trial initiation.

11. SIGNATURE PAGE

Author and Job Title:	Catherine Maidens, Pharmacovigilance Manager
Signature:	DocuSigned by: Catherine Maidens 6A859A9CF4EB497...
Date:	07 May 2024 | 11:25 BST

Authorised by: Name and Job Title	Helen Cadiou, Head of QA
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	07 May 2024 | 15:44 BST

12. SOP TRAINING LOG

	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 of trainee**	**Name of Trainer (if applicable)**	**Signature**	**Date**
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	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 of trainee**	**Name of Trainer (if applicable)**	**Signature**	**Date**
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	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 of trainee**	**Name of Trainer (if applicable)**	**Signature**	**Date**
17							
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