Standard Operating Procedure for the classification, review and submission of clinical trial amendments

SOP ID Number: JRO/SPON/S13/07	**Effective Date:** 27/07/19
Version Number & Date of Authorisation: V07, 27/06/19	**Review Date:** 27/07/22
Please check the JRO website to ensure that this version of the SOP is the current version, **http://www.ucl.ac.uk/jro/ standingoperatingprocedures/document-library** **SOP eDocument kept:** S:_SLMS\RSC_ALL_STAFF\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\Sponsor SOPs\SPON_S13_ SOP for the classification, review and submission of Amendments\SPON_S13_SOP for the classification, review and submission of Amendments V07.doc	

Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JBRU/07/S09/00	26/11/2007	N/A	Ira Jakupovic
JBRU/INV/S03/01	03/07/2008	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	10/01/2010	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

ACRONYMS:

CESP	Common European Submission Platform
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
REC	Research Ethics Committee
RM (ATMP)	Regulatory Manager for Advanced Therapy
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 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 and when applicable Regulation 536/2014 and subsequent relevant SIs. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

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 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.

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.

Sections **6.1** and **6.2** of this SOP are applicable when an external CTU has been appointed by the JRO to perform the duties of the Sponsor; in these cases this SOP will be used in conjunction with the relevant CTU 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**
CI / contractually agreed delegate	Notifies JRO of ALL amendments **before** they are submitted.
CI / contractually agreed delegate	Provides JRO with the completed 'Substantial Amendment Notification Form' from the European Commission website or IRAS, or the 'Notification of Non-Substantial Amendment Form' from the HRA website, (**see section 6.3 and appendix 1)**, 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 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

SRA, RM (ATMP), and/or JRO team members	The documents are reviewed by the JRO as necessary to confirm amendment as **substantial** or **non-substantial**. **European Commission CT1** (2010/C 82/01) document is used as a guidance tool to determine the category of the amendment. HRA guidance on substantial and non-substantial amendments can be found at the following website: https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/ Final decision following review determining **substantial** or **non-substantial amendments** is documented in the Amendment Review Form and signed by the SRA, RM (ATMP) that completes the form (as author). Where the trial is managed by an external CTU/CRO and they have their own amendment review form template this can be used instead. A consideration of the necessity of a new risk assessment is documented in the **Amendment Review Form.** **Additional Considerations:** An amendment must be classified as **substantial** if it includes an update to the **Reference Safety Information** (RSI) for the trial (contained within an IB or SmPC). The submission cover letter must indicate that the RSI is being updated. If the 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 subject 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. A tracked changes version of the IB/SmPC should be provided so differences can be easily viewed. As listed in section 3.1.1 amendments relating to **Investigational Medicinal Product** quality data can be considered as substantial and may require subsequent changes to IMPD if these changes have not already been covered in the submitted IMPD. European Medicines Agency guideline 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
SRA, RM (ATMP), CTOM	Another member of the JRO team then reviews the amendment and Amendment Review Form and counter-signs the form as reviewer. Where the trial is managed by an external CTU/CRO who have prepared the amendment, the SRA / RM (ATMP) reviews as above, completes the Amendment Review Form, signs as author and adds N/A in the reviewer section. There is no need for an additional internal JRO review of the Amendment.
SRA, RM (ATMP)	Final documents are received, reviewed and approved on behalf of the Sponsor. The application form - Substantial Amendment Notification Form or Notification of Non-Substantial Amendment Form is then signed *(where applicable)* by the Sponsor ready for submission.
SRA, RM (ATMP)	The signed Amendment Review Form is provided back to Chief Investigator/ delegate for filing.
SRA, RM (ATMP), and/or JRO team members	A copy of the Amendment Review Form must be filed in the JRO Sponsor File.
CI / contractually agreed delegate	A copy of the Amendment Review Form must be filed in the TMF.

6.3 Submission of Amendments

SRA, RM (ATMP) / contractually agreed delegate	Following review and approval the **SRA, RM (ATMP) / contractually agreed delegate** submits the amendment as described in **Appendix 1: Procedure for submission of amendments and receipt of approvals,** and the following guidance: 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 **Additional considerations:** For substantial amendments, details of any previous **non-substantial amendments** must be included, as applicable, with the submission. Addition of a **new site** or change of **Principal Investigator** should **not** be grouped with other amendments but submitted separately to expedite the review process. Substantial amendments that **only the MHRA** assesses (e.g. IMP quality data) - SRA, RM (ATMP) / contractually agreed delegate only submits the amendment to the MHRA and must notify for information only to the REC in the next substantial amendment to the REC. Substantial amendments that **only the REC** assesses (e.g. facilities for the trial) – SRA, RM (ATMP) / contractually agreed delegate only submits the amendment to the REC and must notify for information only to the MHRA in the next substantial amendment to the MHRA. Where the **Investigator brochure** (IB) update, annual or otherwise, constitutes a **non-substantial amendment** for REC and MHRA and this is the only amendment (e.g. the update to IB does not give rise to updated pharmacy manual or protocol) the updated IB should not be submitted to the **HRA**. For **multicentre trials involving several nations of the UK**, consult IRAS guidance on where to submit the amendment: https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx#Submitting-your-amendment
SRA, RM (ATMP) / contractually agreed delegate	The Log of Substantial and Non-substantial Amendments is updated. Contractually agreed delegate files all submission documents in the TMF and sends copies to the Sponsor. Or SRA, RM (ATMP) file copies of all submission documents in the JRO Sponsor File and provide copies to the CI to file in the TMF as applicable.

6.4 Receipt of Approval, Implementation and Dissemination of Information

SRA, RM (ATMP) / contractually agreed delegate	See **Appendix 1: Procedure for submission of amendments and receipt of approvals**. Following receipt of the categorisation / approval email from

	the HRA the **SRA, RM (ATMP) / contractually agreed delegate** notifies participating sites (NHS R&D and trial teams) and LCRN (if applicable). Notification **email templates** can be found here: https://www.hra.nhs.uk/approvals-amendments/amending-approval/ **HRA** will categorise amendments as below: • **Category A** – Amendment to a research study that ALL participating NHS organisations are expected to consider • **Category B** – Amendment to a research study that only those participating NHS organisations affected by the amendment are expected to consider • **Category C** – Amendment to a research study that participating NHS organisations are not expected to consider If any amendments are **category A** or **B**, sites have 35 days to raise any objections, after which if no objections have been raised, the amendment can be implemented. **Category C** amendments can be implemented immediately. Following receipt of the Approval Letter from the **MHRA** the **SRA, RM (ATMP) / contractually agreed delegate** notifies the CI and any other parties as applicable. Amendments must **not** be implemented until all applicable approvals are in place.
SRA / RM (ATMP)	Updates the Log of Substantial and Non-substantial Amendments with approval dates. Files all approval letters in JRO Sponsor File.
CI/PI/contractually agreed delegate	Files all approval letters in the TMF/ ISF.
SRA, RM (ATMP) / contractually agreed delegate	It is optional for NHS R&D offices to issue a continuing permission document; therefore one may not be received. If a continuing permission document has been received, this must be filed in the TMF and the JRO sponsor file.

6.4.1 Condition Of Approval

SRA, RM (ATMP) / contractually agreed delegate	If approvals with conditions are received from any parties, this is communicated to the CI. Response is required from CI or delegate in writing prior to re-submission.

SRA or RM (ATMP) / contractually agreed delegate	The **SRA or RM (ATMP) / contractually agreed delegate** receives and reviews the response to conditions of approval letter from CI/delegate to ensure all conditions have been addressed. The response is submitted to the applicable party to ensure the amendment is fully approved. All correspondence is filed in the JRO Sponsor File and sent to the CI or delegate to file in the TMF.

7. REFERENCES

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

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

3. https://www.myresearchproject.org.uk

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

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

8. APPENDICES

Appendix 1: Procedure for submission of amendments and receipt of approvals

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

1	Log of Substantial and Non-substantial Amendments
2	JRO Sponsor Amendment Review Form
3	Risk Assessment Review Form Checklist

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.

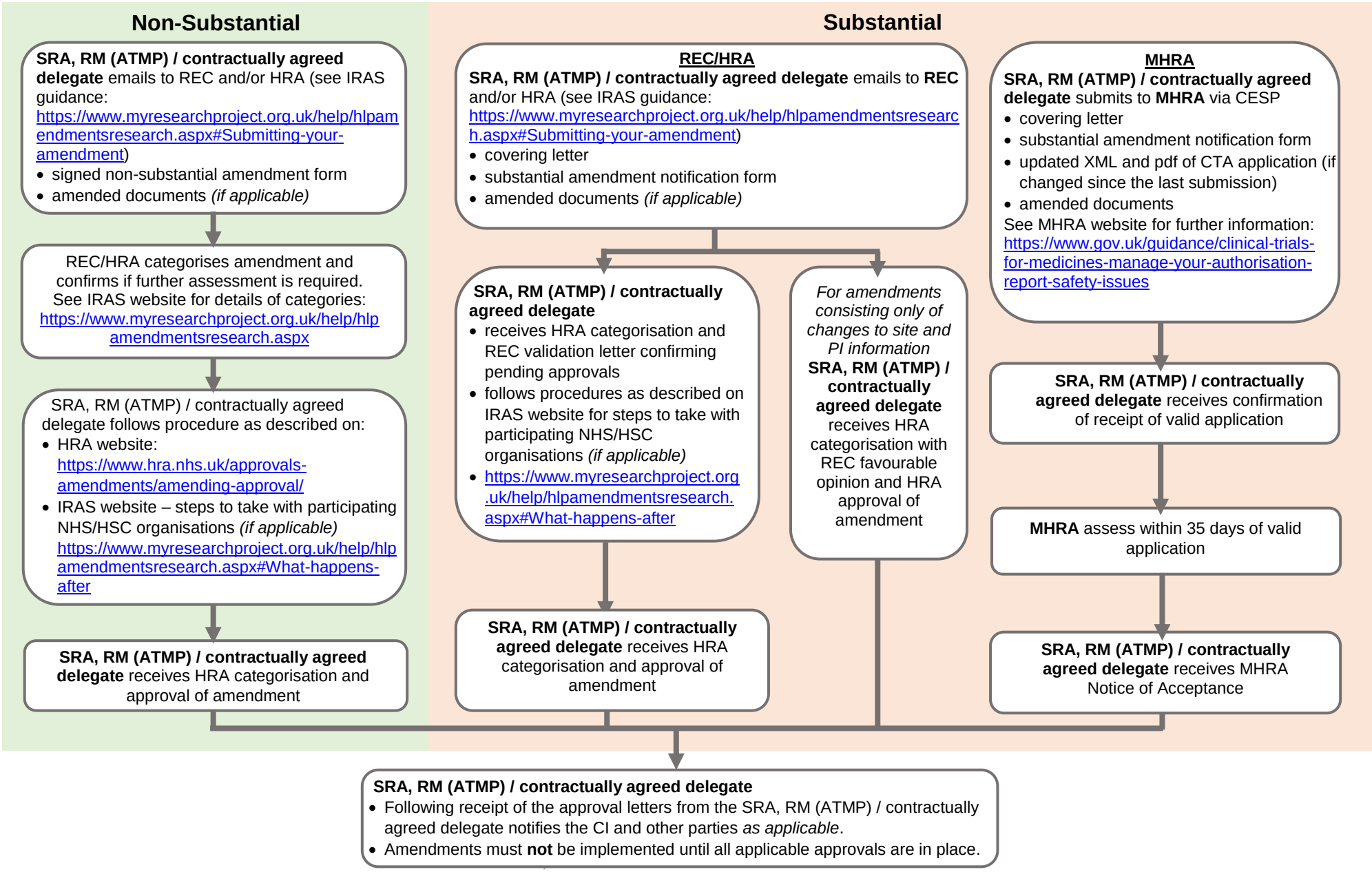
The training will constitute of the person reading the SOP and asking specific questions to the author of the SOP.

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, PV Manager
Signature:	
Date:	
Authorised by: **Name and Job Title**	Helen Cadiou, Head of QA
Signature:	
Date:	

Appendix 1: Procedure for submission of amendments and receipt of approvals



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**
1							
2							
3							
4							
5							
6							
7							
8							

	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**
9							
10							
11							
12							
13							
14							
15							
16							

	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							
18							
19							
20							
21							
22							
23							
24							