Title: Standard Operating Procedure for Reporting Amendments

SOP Number and Version: **UCLH SOP 5**	**Effective Date:** 29/10/2018 **Review Date**: 29/10/2021
For Trust-wide SOPs, please check this is the **latest version of the SOP** on the Joint Research Office website: www.ucl.ac.uk/jro. For Departmental SOPs, please check this is the **latest version of the SOP** with the Research Unit QA Manager.	

Author:
Name: Pushpsen Joshi
Position: JRO Research Governance Manager

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Signature Date

Approved by:
Name: Mona Hassan
Position: JRO Research Quality & Safety Manager

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Signature Date

Authorised by:
Name: Nick McNally
Position: Director of Research Support

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Signature Date

Revision Chronology:

Version Number:	Effective date:	Reason for change:	Author:
1	16th June 2014	Initial standardised SOP for use within UCLH.	Naomi, Heidi, Suzanne
1.1	3rd November 2015	Correction of definition of minor amendments	Mona Hassan
2	6th February 2017	Updated in line with new nationwide HRA amendment processes (effective: 31/03/2016). Removal of references to NIHR CSP amendment processes, which are now obsolete	Mona Hassan
2.1	1st August 2017	Clarification of process concerning costings and contract amendments	Mona Hassan
3	29th October 2018	- Inserted pharmacy review request form for amendments. - Submission of amendments process clarified in SOP and flowcharts, removed any mention of NHS Permission. - Removed 'Receipt of amendment' email template, which is no longer being issued, and updated the 'substantial amendment acknowledgement' email template. Inserted a 'minor amendment' acknowledgement email template. - Inserted clarification that implementation timeframes for amendment at NHS sites are based on HRA Category (A, B, C or new site), irrespective of whether substantial or non-substantial. All category A and B amendments have 35 day implementation timeframes; category C amendments can be implemented as soon as HRA Approval has been received. - Updated definitions and amendment guidance per HRA processes have been included. - Clarification has been provided that delegated Research Units now lead on cost and contract negotiations for amendments, whereas the JRO allocate these to the JRO Costings and Contracts team to review. - Minor clarifications and corrections made throughout document.	Pushpsen Joshi *SOP has additionally been reviewed by:* - *Mona Hassan, JRO RQS Manager* - *Shivali Trivedi, CCTU QA Manager* - *Rhoda Castaneda, CRF Clinical Studies Manager* - *Anna Stockwell, CCTU Clinical Trial Set-up Specialist* - *Cameron Berg, JRO Portfolio Officer.*

ACRONYMS

ARSAC	Administration of Radioactive Substances Advisory Committee
CCTU	Cancer Clinical Trials Unit
CI	Chief Investigator
CRF	NIHR Clinical Research Facility and Leonard Wolfson Experimental Neurology Centre
HRA	Health Research Authority
ISF	Investigator Site File
JRO	Joint Research Office
MHRA	Medicine and Health care Products Regulatory Agency
PI	Principle Investigator
QA	Quality Assurance
REC	Research Ethics Committee
R&D	Research & Development
RN	Research Nurse
RU	Research Unit
SOPs	Standard Operating Procedures
SSD	Service Support Department
TMF	Trial Master File
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust

DEFINITIONS

Clinical Trial of an Investigational Medicinal Product (CTIMP)	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal products(s) and/or Study absorption, distribution, metabolism and excretion of one or more investigational product(s) with the object of ascertaining its (their) safety and/or efficacy.
Sponsor	Individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. A group of individuals and/or organisations may take on sponsorship responsibilities and distribute them by agreement among the members of the group, provided that, collectively, they make arrangements to allocate all the responsibilities in this research governance framework that are relevant to the study.
Health Research Authority (HRA)	The **Health Research Authority** (**HRA**) is an executive non-departmental public body of the Department of Health in the United Kingdom. The HRA exists to provide a unified national system for the governance of health research. **HRA Approval** relates to the current process for the NHS in England that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK research ethics service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England. Further information available at: http://www.hra.nhs.uk/.
NHS Research Ethics Committee (REC)	NHS Research Ethics Committees safeguard the rights, safety, dignity and well-being of research participants, independently of research sponsors. They review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical. RECs are entirely independent of research sponsors, funders and investigators; this enables them to put participants at the centre of their review. RECs review a wide range of research,

	including CTIMPs, qualitative/questionnaire research, research tissue banks, etc. Further information available: http://www.hra.nhs.uk/about-the-hra/our-committees/research-ethics-committees-recs/. All applicable research studies require REC Favourable Opinion to proceed, as do subsequent substantial amendments.
Medicines and Healthcare products Regulatory Agency (MHRA)	The MHRA is an executive agency of the Department of Health in the U.K which is responsible for ensuring that medicines and medical devices work and are acceptably safe. All applicable CTIMP studies and clinical trials require MHRA authorisation to proceed, as do subsequent substantial amendments. Further information available: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
Substantial Amendment	A substantial amendment is defined as an amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree: (1) the safety or physical or mental integrity of the subjects of the trial; (2) the scientific value of the trial; (3) the conduct or management of the trial; (4) the quality or safety of any investigational medicinal product used in the trial. **For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial or not.** Further information available at: https://www.hra.nhs.uk/approvals-amendments/amending-approval/.
Non-Substantial (Minor) Amendments	Defined as any change that does **not** affect: (1) the safety or physical or mental integrity of the subjects of the study; (2) the scientific value of the study; (3) the conduct or management of the study; or (4) the quality or safety of any investigational medicinal product used in the trial. Further information available at: https://www.hra.nhs.uk/approvals-amendments/amending-approval/.
Urgent Safety Measures	The sponsor or investigator may implement appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety (Reg 30), without prior authorisation from a regulatory body or the site's R&D department. However, sponsors/researchers must notify the main REC, HRA and the MHRA (for CTIMPs) immediately and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why. Further information available at: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.

1. BACKGROUND

This Standard Operating Procedure (SOP) describes the processes for how amendments relating to research studies should be reported to the Joint Research Office (JRO), where University College London Hospitals (UCLH) is a research site, and how amendments are processed by the UCLH Joint Research Office and its delegated Research Units

The UCLH Joint Research Office represents the Trust's Research and Development department, and is responsible for issuing UCLH Confirmations of Capacity and Capability for research studies at UCLH (formerly "R&D Approval"), and providing ongoing confirmation for any amendments that may occur. In specific instances, amendment reviews will be delegated to UCLH Research Units via existing arrangements.

This document sets out the procedures to be followed by all staff responsible for submitting and reviewing amendments to research studies run at UCLH.

All SOPs produced should be used in conjunction with UCLH NHS Foundation Trust and University College London policies and procedures. It may be necessary in particular scenarios to also use these in conjunction with Sponsor SOPs and departmental SOPs.

Definition of Amendments
The Health Research Authority (HRA) defines amendments as changes made to a research study after a review body approval has been given. All applicable NHS studies must submit applications for and receive the following approvals in order to proceed with setting up within Trust sites: **HRA approval**, **REC Favourable Opinion**, and **MHRA authorisation** (for CTIMPs/device studies). Once all appropriate regulatory approvals are in place, and NHS sites have completed their Assess, Arrange and Confirm arrangements and confirmed their research Confirmation of Capacity and Capability, any further changes to a study must be prepared and submitted for regulatory and Trust R&D review as an amendment. An amendment can be broadly defined as changes to any of the following documentation:

(i) the terms of the HRA application
(ii) the terms of the REC application
(iii) the terms of the request for clinical trial authorisation from the MHRA (applicable to CTIMPs and device studies only)
(iv) the approved protocol
(v) any other documents submitted with the applications to the HRA, REC or MHRA, or inclusions of new documentation, e.g. changes/updates to study documentation, such as the Participant Information Sheet(s), Consent Form(s), GP letters, Patient Contact cards/Advertisements, Investigator's Brochure, etc.

Substantial and Non-Substantial (minor) Amendments
Amendments are defined as either Substantial or Non-Substantial (i.e. minor) amendments. **For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial or not.**

Substantial Amendment	Non-Substantial (Minor) Amendment
An amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a **significant** degree: (1) the safety or physical or mental integrity of the participants of the study; (2) the scientific value of the study; (3) the conduct or management of the study; (4) the quality or safety of any investigational medicinal product/device/intervention used in the study. Examples: - *Changes to the design or methodology of the study, or to background information affecting its scientific value;* - *Changes to the procedures undertaken by participants; any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;* - *Significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheet for relatives/carers, etc.* Further examples available at: https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments./	Defined as any change that does **NOT** affect: (1) the safety or physical or mental integrity of the participants of the study; (2) the scientific value of the study; (3) the conduct or management of the study; or (4) the quality or safety of any investigational medicinal product/device/intervention used in the study. Examples: - *minor changes to the protocol or other study documentation (e.g. correcting errors, updating contact information);* - *changes to the Chief Investigator's research team (other than appointment of a new Principle Investigator in a CTIMP);* - *inclusion of new sites and investigators in studies other than CTIMPs;* - *extension of recruitment periods or study end dates, etc.* Further examples available at: https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments./

All substantial amendments require approvals from the HRA, REC and MHRA (if applicable), and any other applicable regulatory bodies (e.g. ARSAC, etc.), before they can be implemented in the NHS Trusts where the study is being conducted. In parallel, the R&D offices of the study's sites are additionally expected to review any impact of the amendment **within 35 days of being notified;** this timeline and review consideration is facilitated by the HRA's categorisation process, as below.

Amendments requiring approval **cannot** be implemented until the applicable regulatory approvals are in place, except in the case of urgent safety measures, which may be implemented immediately (with the main REC and MHRA (for CTIMPs) notified within **three days** in the form of a substantial amendment submission).

HRA Amendment Process

In order to streamline and facilitate timely reviews and implementations of study amendments post Trust Confirmation of Capacity and Capability, the HRA put in place an amendment categorisation process that informs R&D departments as to whether an amendment will have any impact that requires consideration of R&Ds and Research Units involved. Amendments have therefore been grouped into three different categories for the purpose of handling them in a manner appropriate to the amendment, regardless of whether they are substantial or non-substantial[1]:

HRA Amendment Categorisation Table

Category	Information
Category A *– Implications for, or affects, all participating NHS/HSC organisations hosting the research project.* *35 day implementation timeframe applies*	This category includes any amendment to a research study that has implications for, or affects, **ALL** participating NHS organisations hosting the research study. All participating NHS organisations will be informed of, and have access to the amendment. All participating NHS organisations are expected to consider the amendment to determine whether they are able to continue confirming NHS Capacity and Capability.
Category B *– Implications for, or affects, specific participating NHS/HSC organisations hosting the research project.* *35 day implementation timeframe applies*	This category includes any amendment to a research study that has implications for, or affects, **SPECIFIC** participating NHS organisations hosting the research study. Only those participating NHS organisations affected by the amendment will be informed of the amendment. However, all participating NHS organisations will have access to the amendment through the relevant national coordinating function. Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue confirming NHS Capacity and Capability.
Category C – no *implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However, the amendment should still be submitted for information.* *As such, the site may implement this amendment* ***as soon as any relevant regulatory approvals are in place*** *(for participating organisations in England, this includes receiving a letter from the HRA Assessment to communicate that you are able to go ahead with the amendment).*	Sponsor/CI are responsible for ensuring all R&Ds and local study teams are informed of category C amendments. Participating NHS organisations are NOT expected to consider the amendment or give continued permission; as such amendments will have no implications for, or affect, the participating NHS organisations hosting the research study. **UCLH request that these are sent to the JRO for information.**

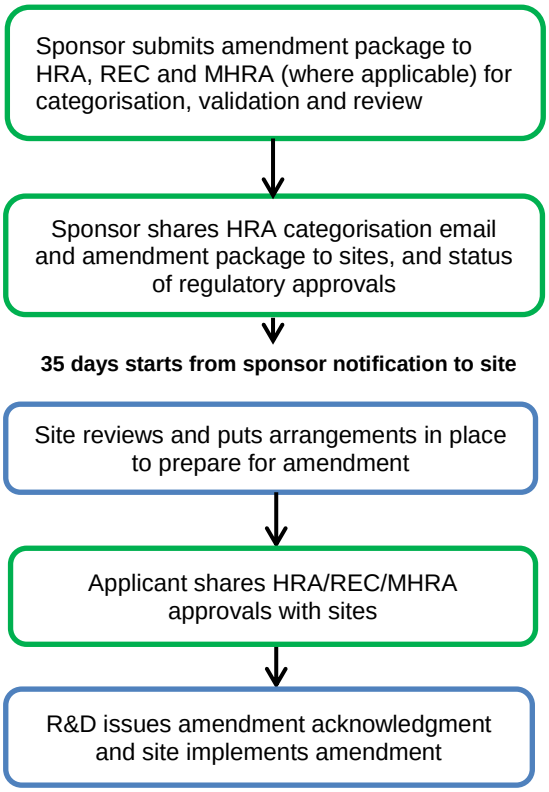
There are additional study related activities and changes that do not require submission as amendments (e.g. GDPR updates in line with HRA guidance, additions of translated versions of

[1] IRAS Amendment guidance: https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

participant facing documentation, etc.). Further examples are available via IRAS (https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx).

This process ensures amendments are handled in a manner that is appropriate to the scale of the amendment and the potential risks to, and the liability of the organisation implementing the amendment, and changes the handling of amendments to 'presumed implementation' following regulatory approval, unless any objection is raised by an NHS organisation within a reasonable time.

It is the HRA's responsibility to issue the amendment categorisation to the applicant, and to provide the amendment implementation date within their categorisation email. The Sponsor must then promptly distribute the amendment categorisation and document package to all applicable sites; sites have 35 calendar days from the date of notification to review the amendment, request more time if required, or raise an objection to Sponsors. An amendment may be implemented by the local study team after 35 days (subject to all applicable regulatory approvals being in place) or if they receive UCLH R&D amendment acknowledgment before this period.



2. PURPOSE

This document defines the Trust's amendment review and approval procedure for changes to research studies following UCLH confirmation of Capacity and Capability. This document sets out the procedures to be followed by all staff responsible for submitting amendments to the Joint Research Office for research studies conducted at UCLH, and covers all research where UCLH is a participating (host) site. These processes are the responsibility of the Chief Investigator/Principle Investigator, who may delegate some or all responsibility of these processes to their study team, but will still hold overall accountability.

This SOP does **not** cover:

- Amendments made during the study's set up, prior to receiving UCLH Confirmation of Capacity and Capability, which should be submitted to the relevant regulatory bodies and the UCLH R&D Portfolio Officer/delegated UCLH Research Unit conducting the study's feasibility and governance review.
- Amendments requiring sponsorship authorisation (pre-submissions to regulatory bodies and NHS sites).

This document only applies to studies currently 'Active' (in recruitment/data collection) within UCLH, and in receipt of UCLH Confirmation of Capacity and Capability.

3. PROCEDURE

Amendment Reporting Process for Substantial and Non-Substantial Amendments to UCLH Studies (please also see flowchart diagram – Appendix A):

	Actions (When? How?)	Responsible persons (Who?)
1	With the exception of **urgent safety measures** (which may be implemented immediately and notified to HRA/REC/MHRA within **3 days**), the Sponsor of a research study is responsible for initiating any amendments to a study and ensuring that all the relevant regulatory approvals have been obtained prior to its implementation. In the first instance, substantial amendment applications must be made to the HRA, the study's REC and other regulatory bodies, where applicable (e.g. MHRA, ARSAC, etc.), for review.	Sponsor
2	The HRA will determine when the amendment can be notified to UCLH as a participating site (e.g. Substantial/Non-Substantial: Category A, B or C). It is then the sponsor's responsibility to distribute the amendment package to all participating sites' R&D departments as soon as categorised, whom will have **35 days** from the date of being notified to review and acknowledge, or to raise an objection.	Sponsor/PI/ Study Team
3	In order to notify UCLH, the complete amendment package should be submitted to the JRO inbox (uclh.randd@nhs.net), and/or the delegated RU. This should include: - HRA categorisation email - Fully signed IRAS Notice of Substantial Amendment form (NOSA) - **Clean** and **tracked** versions of the revised documentation (e.g. Protocol, Participant Information Sheet, Consent form, etc.)	CI/PI/Sponsor /Study team

	- **Updated costing template/information if there are cost implications** The following approval letters (where applicable), must be submitted to the JRO inbox uclh.randd@nhs.net and/or the delegated RU as soon as issued, as the related amendment cannot be approved or implemented without: - HRA categorisation email and HRA Approval email - REC Favourable Opinion letter - Any other applicable regulatory approval letters (e.g. MHRA authorisation, ARSAC approval, etc.)	
4	Upon receipt of an amendment package, a JRO coordinator will first screen the study (via the research study database) to determine whether it is for a study occurring within a delegated Research Unit (RU), and will allocate to the appropriate Unit for review, whom have been formally delegated this review function on behalf of the JRO. If applicable, the JRO will forward the amendment package to the appropriate Unit. The JRO/delegated (RU) will review the amendment and identify any potential issues that may impact supporting departments (e.g. pharmacy or radiology), study finances, study contracts, or governance. In some instances, Sponsors may send amendments directly to RUs for review.	JRO/ delegated Research Unit
5	The 35 calendar day amendment review period starts from the date of the sponsor's email notification (for category A and B amendments). The JRO/delegated RU has 35 days to raise any objections, request more time, or notify the PI/Sponsor of no objection to the amendment being implemented at the site. If there are changes that affect a Service Support Department (SSD), the JRO/delegated RU will request a review from the affected SSD and await their approval before implementing the amendment. If a potential finance, contract or governance impact is identified as a result of the amendment, the JRO/delegated RU will inform the PI/Sponsor immediately. Resolution of governance issues will be sought directly with Sponsors but the issue may be escalated to or throughout the JRO, as appropriate. The JRO will notify the JRO Costings and Contracts team of amendments that potentially impact finances and/or contracts, which will be negotiated and agreed directly between the JRO Costings and Contracts team and the Sponsor. Delegated RUs will however lead in finance/contract negotiations with the sponsors; if sponsors have provided written confirmation that revised costs/contract has been approved, the related substantial amendment may be acknowledged by the JRO, while the contract amendment is executed separately. Once this is agreed, the JRO/delegated RU will be notified for their records. If cost negotiations have not been agreed, and the amendment will pose significant implications for UCLH, the JRO/delegated RU may raise an amendment objection to Sponsors. Otherwise, provided no logistical, safety or governance concerns have been raised by the JRO/delegated RU at the time of identifying the potential finance and/or contract implications, the JRO will seek to acknowledge the amendment following receipt of the amendment bundle and the new financial/contract arrangements will continue to be negotiated separately by relevant	JRO/delegated Research Unit

	personnel.	
6	Once amendment is reviewed and no issues identified (and an approval bundle amendment package returned by the relevant RU, if applicable), the JRO will send out a **'No Objection email'** (see Appendices B & C)	JRO
7	If 35 days passes with no communication from the JRO/delegated RU, then the amendment may be implemented at UCLH without acknowledgement (as per HRA guidance). However, regulatory approvals **must** be in place before an amendment can be implemented (the only exception to this rule is an **urgent safety measure)**.	PI/Sponsor/Study Team
8	The PI/delegated study team are responsible for localising the appropriate amendment documentation before implementing at the site, and updating the ISF/TMF, and ensuring all staff are made aware.	PI/Study Team

4. IMPLEMENTATION & TRAINING

Staff following this SOP shall confirm they have read and understood the procedures outlined above by completing their relevant signature log as a record of acknowledgement. It may be necessary to ensure staff are trained in using specific SOPs.

5. PUBLICATION & COMMUNICATION

This SOP is authorised and published on the JRO website: http://www.ucl.ac.uk/jro. The latest version of the SOP will be made available on the JRO website.

The original fully signed master copy is stored in a designated binder within the JRO and maintained by the JRO Research Quality & Safety Manager (or Research Unit QA Manager if a Departmental SOP).

6. REFERENCES

Joint Research Office:
www.ucl.ac.uk/jro

Health Research Authority:
http://www.hra.nhs.uk/

Health Research Authority Amendments Guidance:
https://www.hra.nhs.uk/approvals-amendments/amending-approval/
https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/
https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx
http://www.hra.nhs.uk/about-the-hra/our-committees/research-ethics-committees-recs/

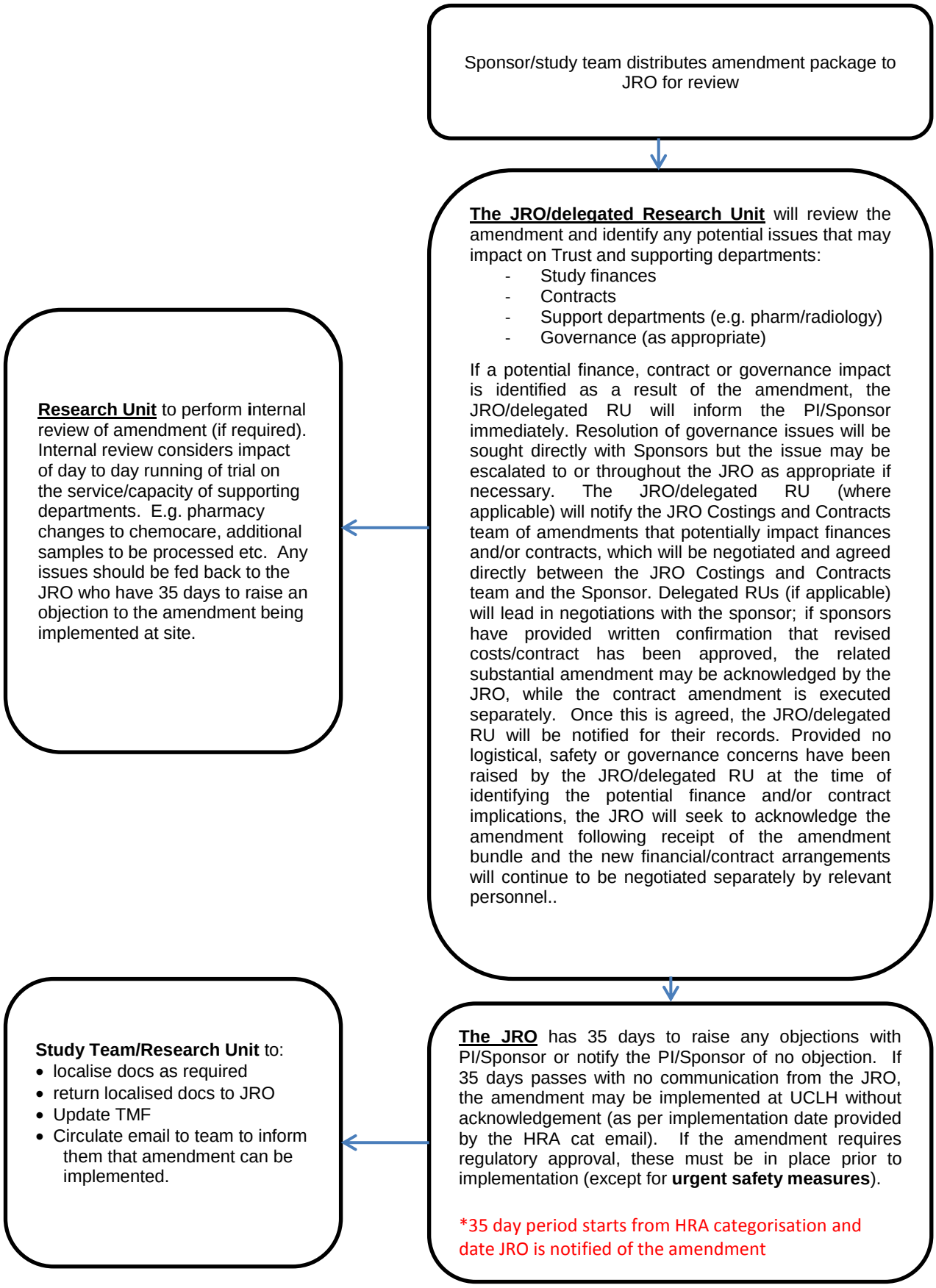
MHRA and MHRA Amendments Guidance:
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#apply-to-change-your-trials-protocol-or-documentation

IRAS Amendment Guidance:
https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

7. APPENDICES

Appendix A – Amendments Flowchart from Sponsor to Site (UCLH)
Appendix B – JRO Acknowledgement of a Substantial Amendment Email Template
Appendix C – Acknowledgment of Non-Substantial Amendments Email template
Appendix D – Delegated Research Unit Amendment Process
Appendix E – Pharmacy Amendment Review Email Template

Appendix A –Amendments Flowchart from Sponsor to Site (UCLH)



Appendix B – JRO Acknowledgement of a Substantial Amendment Email Template

Dear ##RECIPIENTS_NAME##,

Project ID: ##/#### (Please quote in all correspondence)
IRAS ID:
REC Ref:
Title:
Amendment: Substantial Amendment
Date of HRA categorisation:

Confirmation of Amendment Capacity & Capability

The UCLH/UCL Joint Research Office (JRO) acknowledges receipt of the above amendment and the following documents:

a. REC approval letter dated and therein listed documents
b. MHRA acceptance letter dated
c. HRA amendment approval email dated

The JRO has no objections to this amendment and the study may continue at UCLH.

You must ensure that you localise all patient facing documentation prior to consenting participants; this will be subject to random audit checks.

Please forward this email on to all relevant parties involved with this study at UCLH.

Please insert a copy of this email in your site file.

Many thanks.

****Please note we will NOT be issuing a separate hard copy/electronic R&D Acknowledgment letter; please accept this email as approval of amendment implementation at UCLH.**

Appendix C – Acknowledgment of Non-Substantial Amendments Email template

Dear ##RECIPIENTS_NAME##,

Project ID: XX/XXXX (Please quote in all correspondence)
IRAS ID:
REC Ref:
Title:
Non-substantial
Amendment:

Confirmation of Amendment Capacity & Capability

The UCLH/UCL Joint Research Office (JRO) acknowledges receipt of the above mentioned amendment.

We have reviewed the amendment, including the HRA Categorisation email dated DD/MM/YYYY (noting the minor amendment) and therein listed documents, and the HRA Approval email dated DD/MM/YYYY [delete if not issued].

The JRO has no objections to this amendment and the study may continue at UCLH.

If applicable, you must ensure that you localise all patient facing documentation prior to consenting participants; this will be subject to random audit checks.

Please forward this email on to all relevant parties involved with this study at UCLH.

Please keep a copy of this email for your site file.

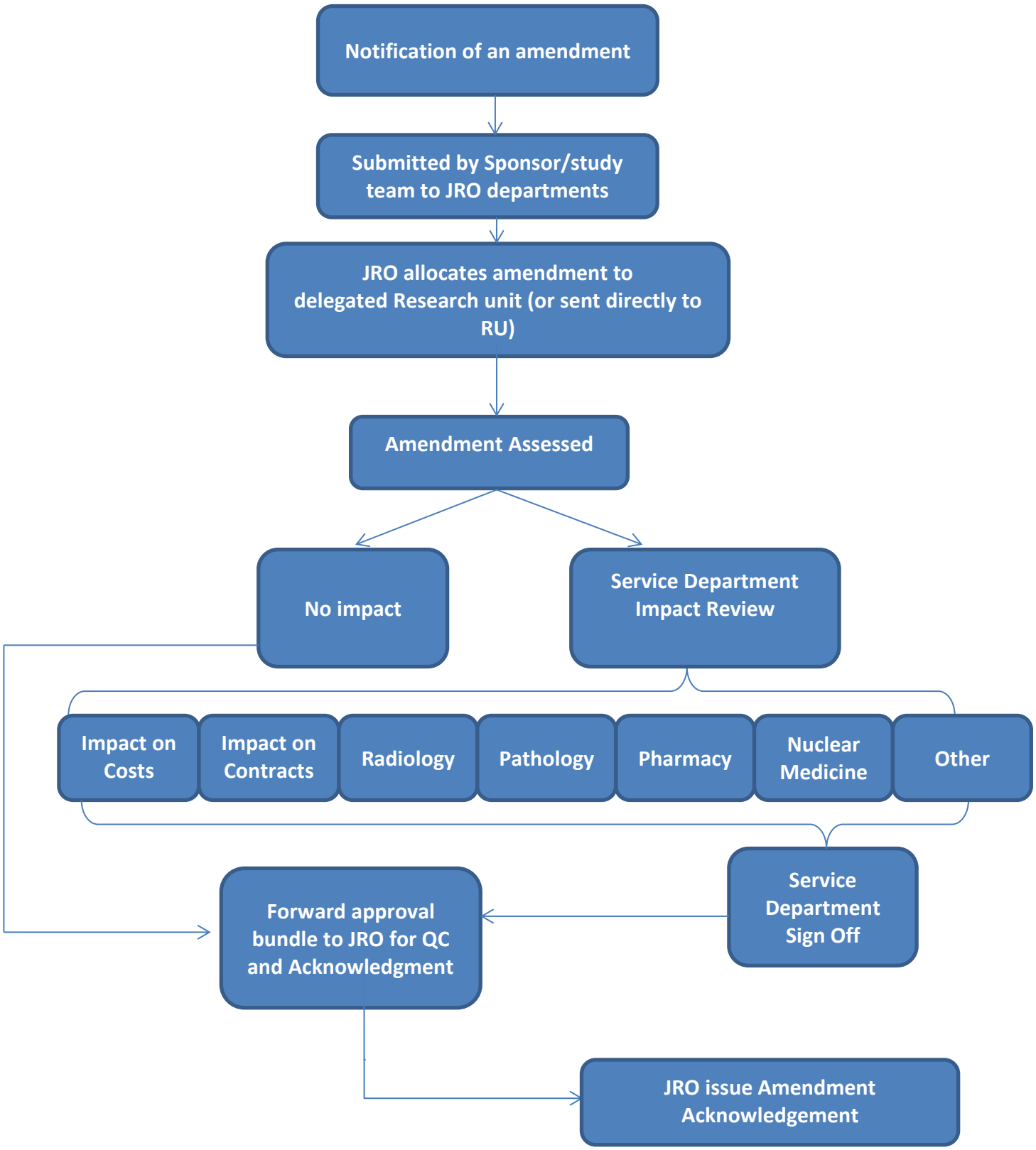
Best wishes with your research.

Kind regards,

[insert signature]

****Please note we will NOT be issuing a separate hard copy/electronic R&D Acknowledgment letter; please accept this email as approval of amendment implementation at UCLH.**

Appendix D – Delegated Research Unit Amendment Process



Appendix E – Pharmacy Review Request Email Template

Short Trial Title:	
Full Title:	
Principal Investigator:	
R&D Ref:	
IRAS Number:	
Amendment Number:	
Date of HRA Categorisation:	
Date of REC Approval Letter:	
Date of MHRA Approval Letter:	
Date of HRA Confirmation:	
List of New Documents as a result of the Amendment:	
Trial Status (*e.g. open, closed etc*)	
No. of Active patients	