Standard Operating Procedure for granting UCL sponsorship for Clinical Trials of Investigational Medicinal Products (CTIMPs)

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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JBRU/SPON/S07/00	15/10/2008	N/A	Joanna Galea-Lauri, Nicky Gower, Sue Kerrison
JBRU/SPON/S07/01	10/01/2010	Update SOP to reflect changes in the first contact questionnaire. Clarification of use of risk assessment template to identify trial risk. Format amended in line with revised SOP on SOPs to incorporate a UCL only logo, an Acronyms table, eDocument file path, associated templates/log table, SOP dissemination and training and a signature page. Slight change of title: SOP to be used by Sponsor when assessing risk factors in CTIMPs Sponsorship decision instead of "SOP to be used by Sponsor when assessing risk factors in Sponsorship decision for CTIMPs"	Suzanne Hodgson
JBRU/SPON/S07/02	11/01/12	Due for review. NO CHANGES made as this SOP will be merged with a SOP which is in draft	Same as above, as NO CHANGES
JBRU/SPON/S07/03	16/06/12	SOP Standard Operating Procedure for using the UCL First Contact Questionnaire and CTIMP Protocol Template (JBRU/INV/S01/02) has been superseded by this SOP and is now obsolete. Title of SOP also updated SOP updated to cover all processes involved in UCL sponsorship decision, including costings, protocol review and completion of risk assessment template. Updated to include appointment of UCL as a Legal representative	Alison Evans
JRO/SPON/S07/04	17/06/15	Added JRO peer review procedures Added Initial risk assessment process and template.	Gemma Jones
JRO/SPON/S07/05	29/06/18	Amended insurance confirmation process to align with insurance SOP and inserted flow of information to the JRO Data team.	Nimrita Verma

ACRONYMS:	
ATMP	Advanced Therapy Medicinal Products
BSG	Biostatistics Group (JRO)
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTOM	Clinical Trials Operations Manager
COA	Compliance Oversight Advisor
DIO	Data Information Officer

EEA	European Economic Area
EU	European Union
FCQ	First Contact Questionnaire
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
JRO	Joint Research Office http://www.ucl.ac.uk/jro/
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
QA	Quality Assurance
RA	Risk Assessment
RM	Regulatory Manager
SOC	Sponsor Oversight Committee
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
UCL	University College London
UCLH	University College London Hospital NHS Foundation Trust
UK	United Kingdom

Standard Operating Procedure for granting UCL sponsorship for Non-Commercial Clinical Trials of Investigational Medicinal Products (CTIMPs)

1. PURPOSE

This standard operating procedure (SOP) describes the activities undertaken by the Joint Research Office (JRO), to grant sponsorship for Clinical Trials of Investigational Medicinal Products (CTIMPs). The sponsorship pathway comprises five defined stages which all CTIMPs must progress through, to obtain sponsorship from University College London (UCL).

This SOP also outlines the process for studies whereby UCL agree to act as EU Legal Representative on behalf of a Sponsor based outside of the European Economic Area (EEA).

2. JOINT UCLH/UCL RESEARCH OFFICE 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.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/20/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)".

This SOPs refers to the UCL sponsorship decision process (or agreement to act as EU legal representative) for CTIMPs only.

A **clinical trial** is defined as any investigation in human subjects, other than a non-interventional trial, intended—
(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
(b) to identify any adverse reactions to one or more such products, or
(c) to study absorption, distribution, metabolism and excretion of one or more such products, with the object of ascertaining the safety or efficacy of those products;
(Ref: Article 2 of Directive 2001/20/EC)

Every clinical trial must have a named Sponsor. A Sponsor is defined in Article 2(e) of Directive 2001/20/EC as "an individual, company, institution or organisation which takes responsibility of the initiation, management and/or financing of a clinical trial". As per the Clinical Trial Regulations (SI 2006/1928) 'a person who is a Sponsor of a clinical trial may delegate any or all of his functions under these Regulations to any person, but any such arrangement shall not affect the responsibility of the Sponsor'.

Protocol review
The protocol for a CTIMP must be written in accordance with applicable guidelines and regulations. For UCL sponsored CTIMPs it is a requirement to use the JRO protocol template which has been written in compliance with these guidelines and regulations.

Risk assessment
A research protocol will always carry an element of risk, which in this case is taken to mean the potential risk to the safety and rights of the research subject, risks to the reliability of the trial results and risks to the Sponsor's institution. A comprehensive risk assessment to identify the inherent risk of a trial is carried out by the JRO prior to UCL sponsorship approval.

Specific factors which are deemed to be risks are outlined in the "**JRO CTIMPs risk assessment template**" which the JRO uses to assess risk.

Factors that are likely to pose risk in the conduct of a trial include:

- Involving a medicinal product not licensed in any EU Member State
- Trials that are excluded or restricted in terms of insurance
- Insufficient funding
- Certain groups of patients e.g. pregnant women, children, vulnerable adults.
- CI's lack of trial experience
- Trial complexity in terms of design, size and involvement of multi-centre and/or multinational trials

The risk assessment process is completed to identify potential vulnerabilities in trial design and methodology, including IMP risk, and to prepare a management plan to minimise the risks, and facilitate a risk-proportionate approach to the trial activities.

EU legal representative
If the main Sponsor of a clinical trial with a medicinal product is not based in the European Economic Area (EEA), it is a statutory requirement to appoint a legal representative based in the EEA for the purposes of the trial.

The legal representative:

- should be willing to act as the agent of the Sponsor in the event of any legal proceedings instituted in the EEA (for example, for service of legal documents)
- does not assume any of the legal liabilities of the Sponsor(s) for the trial by virtue of the role of legal representative and does not therefore require insurance or indemnity to meet such liabilities but may in some cases enter into specific contractual arrangements to undertake some or all the statutory duties of the sponsor in relation to the trial, in which case the legal representative would also be regarded as a co-sponsor and would then require insurance or indemnity cover.

In all trials for which UCL agrees to act as EU legal representative, a contract will be put in place with the sponsor to detail the responsibilities UCL have agreed to undertake on behalf of the Sponsor.

4. SCOPE OF THIS SOP

This SOP describes the JRO process for granting UCL sponsorship for JRO-managed CTIMPs, or for agreement of UCL to act as EU Legal Representative of JRO-managed CTIMPs.
The following processes take place, defined as Stages 1 – 5:

Stage 1: Determine study categorisation and appropriate regulatory framework and governance processes to be implemented (note this SOP covers CTIMPs only).

Stage 2: Request and receipt of initial study information.

Stage 3: Undertake costings to identify the resources and required finances to complete the trial, and confirmation of funding awarded.

Stage 4: Review the trial protocol to ensure it meets appropriate standards and corresponds to the UCL protocol template.

Stage 5: Risk assessment of the trial to identify the risks associated with the trial and appropriate risk mitigation strategies, and, if appropriate, full committee approval of UCL sponsorship, issue of a full sponsorship letter or confirmation of agreement to act as EU legal representative.

Please refer to SOP SPON/S27 for the procedure on taking over sponsorship of a CTIMP from another sponsor organisation.

Please refer to SOP SPON/S28 for full procedure on ensuring a CTIMP is covered by UCL insurance.

5. RESPONSIBLE PERSONNEL

The decision to grant UCL sponsorship, or act as EU legal representative, is based on a procedure involving the multidisciplinary team at the JRO.

The roles and responsibilities of individual JRO staff are detailed in the table found in section 6 of this SOP.

For clinical trials of advanced therapy medicinal products, the duties of the SRA shall be undertaken by the Regulatory Manager (ATMP).

6. PROCEDURE

6.1. Stage 1: Confirm Study Category

	Responsibility	Undertaken by	Activity
1	JRO	SRA	Receive initial contact from Investigator. Confirm study meets the definition of a CTIMP if this has not already been confirmed. Please refer to SOP SPON/S23 for the JRO procedure on identification and classification of studies as CTIMPs. If additional clarification is required, ensure documented evidence is obtained to support the decision (i.e. email from MHRA).

6.2 Stage 2: Obtain initial study information

The aim of this stage is to obtain initial study information to undertake an appropriate preliminary costing of the study (Stage 3) for the purposes of obtaining a grant.

For legal representative trials, the extent of study information obtained should establish and be proportionate to the responsibility(ies) UCL are undertaking in the role of legal representative.

	Responsibility	Undertaken by	Activity
1	JRO	SRA	Send first contact template email with First Contact Questionnaire (FCQ) and appropriate protocol template (CTIMP or ATMP) to Investigator. Add basic trial information onto trial spread sheet.
			Issue trial statistician's engagement letter template to Investigator (for the nominated external statistician to complete) OR, if JRO Biostatistics Group (BSG) collaboration is required, advise the Investigator to contact the BSG administrator directly to arrange a meeting. *Note: Above is applicable for sponsorship requests only.*
			Identify if the trial will have peer review as part of the grant application. If not, instruct the investigator to organise the proposal to undergo 2 independent peer reviews and provide copy of JRO Peer Review policy (n/a for legal rep trials)

6.3 Stage 3: Costing Review

Costing will be generated based on information provided from Stage 2. Any subsequent changes to the study design, management etc. may impact on the overall costs and sponsorship decision and further adjustments may be required.

For legal representative trials costing will be completed as appropriate depending on the delegated responsibilities of the JRO.

	Responsibility	Undertaken by	Activity
1	JRO	SRA/RM	Receive completed FCQ, signed trial statistician's engagement letter and summary protocol/synopsis. Review submitted documents for completeness and seek clarification from the Investigator as required.
2	JRO	SRA/RM/Data Information Officer (DIO)	Register study on ReDA and allocate JRO sponsor/legal representative number. Update tracking spreadsheet and inform Investigator of registration and sponsor/legal representative number (SRA/RM).
3	JRO	SRA/BSG/ RM (Pharm)/ COA	For sponsorship requests send signed trial statistician's engagement letter, first contact questionnaire and summary protocol to the BSG clinical trial lead for review. The BSG will review whether the named statistician is adequately qualified and engaged with the study and that they are responsible for the sample size calculation. Send protocol to relevant JRO staff to assess protocol requirements and impact on cost (e.g. RM (Pharm) or review of IMP requirements, and COA to assess monitoring requirements).
4	JRO	SRA/ RM/JRO CTIMPs team	Complete SOC Risk Assessment for the trial using the JRO template.
			Review SOC Risk Assessment at the Clinical Operations Meeting. If considered necessary based on anticipated risk, the trial will be referred to Sponsor Oversight Committee (SOC).
5	JRO	SRA/RM/ Finance/ Investigator	Arrange review/meeting with JRO trials team, finance team, Investigator and Central Finance Unit (if applicable) to identify study costs. For legal representative studies the appropriate legal representative fees and cost associated with activity delegated to UCL will be agreed.
6	Site	Investigator	Investigator to develop costings based on advice from costings meeting.
7	JRO	SRA/RM/ Finance team	Receive Investigator costs. Review and approve costs with JRO finance.
8	JRO	Finance team	Authorised JRO signatory signs off costings for study.
9	JRO	SRA/RM	Send JRO finance sign-off to Investigator and "in principle" sponsorship letter (for purposes of grant application) signed by authorised JRO signatory.
10	JRO	SRA/RM	Request copy of final grant application.
11	JRO	SRA/RM	Await outcome of grant award. Follow up with

			Investigator on an approximate three-monthly basis to track progress of grant application.
12	JRO	SRA/RM	File correspondence in the sponsor pre-award file.
13	JRO	SRA/RM	Receive confirmation of grant award from Investigator. If potential shortfall in funding is identified (e.g. full award not given), funding will be reviewed internally at JRO and, if required, referred to SOC.
14	JRO	SRA/RM	Ensure peer review has been conducted.
15	JRO	SRA/RM	Set up sponsor file (paper) in accordance with JRO SOP S11. For legal representative trials a sponsor file should be set up with sections proportionate to the delegated responsibilities of the JRO.

6.4 Stage 4: Protocol Review (wait for funding to be obtained, prior to starting this step)

Note: For legal representative requests, undertake a review of the full protocol at this stage to ensure the protocol is compliant with EU and UK Clinical Trials Legislation. A UK addendum to the Protocol may be the most appropriate way to incorporate UK specific information.

	Responsibility	Undertaken by	Activity
1	JRO	SRA/RM	Request draft protocol (completed using JRO protocol template) and applicable supporting documents from Investigator.
2	JRO	SRA, RM (Pharm), Pharmacovigilance manager, COA, BSG	Upon receipt of completed protocol template send protocol and supporting documents to the BSG for review **and in parallel** undertake protocol review across JRO trials team.
3	JRO	SRA/RM	Return consolidated protocol comments to Investigator. BSG may correspond with Investigator directly.
4	JRO	SRA/RM	Receive amended draft protocol, confirm standard of protocol is compliant with the regulations and sufficient (including approval of the BSG) to complete the risk assessment (RA). Continue with steps 3 and 4 until consensus reached. Final draft of protocol approved.
5	JRO	SRA/ RM/CI	Ensure final protocol signed by Investigator and JRO authorised signatory.

Note: During protocol review stage, send out documents that are required for final sponsorship approval, e.g. insurance registration form and CI agreement. Also send Site Feasibility Questionnaire, Managing Organisation Suitability Questionnaire,

Pharmacy Site Assessment Questionnaire and Laboratory Feasibility Questionnaire, as applicable. For legal representative requests initiate legal representative agreement via JRO contract manager.

6.5 Stage 5: Risk Assessment and Sponsorship/ Legal Representative Approval

	Responsibility	Undertaken by	Activity
1	JRO	SRA/RM/Clinical Trials Operations Manager (CTOM)	Complete RA using JRO RA template. Review completed RA in Clinical Operations Meeting or another appropriate group. Finalise RA and sign off.
2	JRO	SRA/RM	Trials may need to be referred to the SOC depending on the outcome of the RA (and if there have been significant changes since a SOC review during costing review (see section 6.3). Inform Investigator of outcome of RA or referral. For legal representative requests ensure decision has been approved either via the Clinical Operations Meeting or SOC.
3	JRO	SRA/RM	Ensure insurance confirmation letter has been issued, and the Chief Investigator has signed the CI agreement. **Note: The JRO will not issue an insurance confirmation letter for trials which do not require automatic referral to the insurers. This denotes acceptance that the trial is insured under the existing terms of the policy.**
4	JRO	SRA/RM	Issue full sponsorship letter (signed by JRO authorised signatory) and fully executed CI agreement, or notify Investigator of decision to decline sponsorship, as applicable. Ensure Investigator informed of any conditions attached to sponsorship approval.
5	JRO	SRA/RM	For requests for EU legal representation: issue Legal Representative letter (signed by JRO authorised signatory) and ensure legal representative contract is in place. Alternatively inform Sponsor that JRO declines taking on legal representation for their trial.
6	JRO	SRA/RM	File all relevant information in the sponsor/legal representative file and update trial spreadsheet.

7	JRO	SRA/RM	Send a copy of the following documentation to the JRO Data Team: • Completed FCQ • Signed Sponsorship in Principle letter • Signed Full Sponsorship Letter/Legal Representative Letter • CI agreement • Confirmation of Funding letter

Note: It is important to note that if there is substantial amendment that is likely to affect to a significant degree, the safety or integrity of patients or the management of the trial, there may be a need to readdress the risk assessment and/ or costing of the trial. Following issue of a full sponsorship letter, if a change is made which significantly affects the trial design, it may be necessary to repeat applicable stages of this SOP.

7. REFERENCES

MHRA website:
https://www.gov.uk/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

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

ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (1996)

Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031) as amended.

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

8. TEMPLATES/LOGS ASSOCIATED TO THIS SOP

JRO Templates http://www.ucl.ac.uk/jro/

1	SOP training log (Section 12 of each SOP),
2	First Contact Questionnaire
3	Protocol template
4	Statistician's engagement letter template
5	UCL costings template
6	Sponsorship letters (in principle and full)
7	Legal Representative letter
8	Chief Investigator Agreement template
10	Managing Organisation Suitability Questionnaire
12	Laboratory Feasibility Questionnaire
13	SOC Risk Assessment template

14	JRO CTIMPs Risk Assessment template

UCL SOPs/ policies:

1	SPON/S27: Standard Operating Procedure for Transfer of CTIMP Sponsorship to UCL.
2	SPON/S28: Standard Operating Procedure for Insuring Clinical Studies Sponsored or managed by UCL.
3	SPON/S23: Standard Operating Procedure for identifying Clinical Trials of Investigational Medicinal Products.
4	SPON/S11 Standard Operating Procedure for the Preparation of the JRO Sponsor File for UK Clinical Trials
5	JRO Peer review procedures for Sponsored Studies

9. SOP DISSEMINATION AND TRAINING

SOPs will be distributed to the relevant staff, by the named author on the front page of the SOP. Staff 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.

10. SIGNATURE PAGE

Author and Job Title:	Nimrita Verma , Sponsor Regulatory Advisor/Device Lead
Signature:	
Date:	22/06/2018

Authorised by: **Name and Job Title**	Helen Cadiou, Head of QA
Signature:	
Date:	22/06/2018

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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