Standard Operating Procedure for Oversight and Monitoring of UCL Sponsored CTIMPs

SOP Number: JRO/SPON/S19/06	**Effective Date:** 12/07/19
Version Number & Date of Authorisation: V06,12/06/19	**Review Date:** 12/07/22
SOP eDocument kept: S:\SLMS_RSC_ALL_STAFF\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\Sponsor SOPs\SPON_S19_ SOP for oversight and monitoring of UCL sponsored CTIMPs\SOP 19\SPON_S19_SOP for oversight and monitoring of UCL sponsored CTIMPs_V06.docx	

Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JRO/08/S09/00	21/05/08	N/A	Joanna Galea-Lauri
JRO/SPON/S19/01	15/10/08	To implement a new numbering system and formatting changes by Ira Jakupovic to comply with the SOP on SOPs (JRO/SPON/S01/02). The content of this SOP was not affected. SOP ID numbers that refer to Central Monitoring SOP and TMF SOP have also been changed to reflect a new numbering system that has been applied to all SOPs.	Joanna Galea-Lauri
JRO/SPON/S19/02	14/02/10	To implement the UK regulations Compliance form (Part 2) for all active trials and outline the procedure for the extent and frequency of use. To outline the review process of the forms by the JRO and requirements for sign off with an agreed CAPA plan. 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, e-Document file path, associated templates/log table, SOP dissemination and training and a signature page.	Ann Cochrane and Gurjinder Kahlon
JRO/SPON/S19/03	13/01/12	To update the processes	Shruti Aggarwal & Gurjinder Kahlon
JRO/SPON/S19/04	12/01/15	To remove Compliance form (part 1) as this is now associated with SOP20 To clarify the process and define clearly between central and on site monitoring processes To clarify the process for review of multi centre trials.	Gemma Jones
JRO/SPON/S19/05	13/01/18	To further clarify the process required for on-site on central monitoring. To further clarify the role of a COA in detail. Editing Appendix 1 to coincide with information in the Monitoring Plan and Compliance Form templates.	Michelle Tu
JRO/SPON/S19/06	12/07/19	• Clarification of the process for central monitoring • Removal of the requirement to complete the Telephone/Oversight form for Phase IIb studies unless currently required by the UCL JRO Oversight/Monitoring Plan for a study	Michelle Barber

		• Update to text in template email, see Appendix 2 • General administrative changes and updates to document names throughout	

ACRONYMS:	
ATMP	Advanced Therapy Medicinal Product
CAPA	Corrective and Preventative Action
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF	Case Report Forms
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTOM	Clinical Trials Operations Manager
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
JRO	UCL Joint Research Office http://www.ucl.ac.uk/jro/
MHRA	Medicines and Healthcare Products Regulatory Agency
MVR	Monitoring Visit Report
PI	Principal Investigator
QC	Quality Control
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SRA	Senior Regulatory Advisor
TMF	Trial Master File
UCL	University College of London

Standard Operating Procedure for Monitoring of UCL Sponsored CTIMPs

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for retaining oversight and performing monitoring of CTIMPs sponsored by UCL.

Please check that you are reading the latest version of this SOP: http://www.ucl.ac.uk/jro/

2. JOINT UCLH/UCL Research Office

All SOPs are produced, reviewed and approved in accordance with the JRO SOP on 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. For convenience, this document will use the term ‘Regulations’ to cover the requirements of the UK SI legislation.

UCL has implemented an oversight process for CTIMPs sponsored by UCL. This process is driven by a risk-based monitoring strategy (**Appendix 1**).

For higher-risk trials, the sponsor will ensure frequent on-site monitoring is conducted. For lower-risk trials, on-site monitoring is less frequent, though the sponsor has developed the PI Oversight form/UK Regulation Compliance form (PART 2) to assist CI/PIs (depending on monitoring risk assessment of trial) to actively maintain and demonstrate oversight of the trial during its conduct phase.

3.1 Definitions

CAPA: The Corrective and Preventative Action necessary to address any shortcomings highlighted during the monitoring process including (but not limited to) review of the PI Oversight form/UK Regulation Compliance form (PART 2). Corrective Action is the action to eliminate the cause of a detected fault or deviation. Preventative Action is the action to eliminate the cause of a potential non-conformity or other undesirable potential situation. Preventive action is taken to prevent re-occurrence.

Findings: Results of the evaluation of the collected evidence against set criteria. This could be from on-site monitoring or sponsor review of the PI Oversight form/UK Regulation Compliance form (PART 2) against the protocol, GCP, UK Regulations and sponsor/investigator SOPs.

Monitoring A quality control (QC) activity which involves a system of ongoing checks to detect faults and failures in order to correct them, and prevent the failure from recurring so that the specified output is produced consistently, in this context compliance with the UK Regulations, Sponsor SOPs, approved protocol and GCP.

UCL JRO Oversight/ Monitoring Plan: The agreed system for monitoring a CTIMP as referenced in the protocol at the frequency determined by the *risk based monitoring strategy* (Appendix 1).

4. SCOPE OF THIS SOP

This SOP outlines the procedures to be used for the oversight of CTIMPs Sponsored by UCL and where Sponsor responsibilities are managed by the JRO. This includes the process for Trial specific UCL JRO Oversight/ Monitoring Plans, PI Oversight form/UK Regulation Compliance form (PART 2) completion and review, as well as procedures to be followed during a site visit by a sponsor representative.

Monitoring of studies outside the UK will not be addressed in this SOP. This will be defined in trial specific contracts.

5. RESPONSIBLE PERSONNEL

Chief Investigator (CI): ensures that the PI Oversight form/UK Regulation Compliance form (PART 2) is maintained *and* returned to the sponsor for review, at the frequency agreed at the start of the trial and in the UCL JRO Oversight/ Monitoring Plan. The CI must also ensure all outstanding actions documented in the Monitoring Visit reports for their site (as PI) are completed and help where needed with closing other sites Monitoring Visit report actions.

Principal Investigator (PI): (In a multicentre trial) responsible for the completion (or delegation of completion at site) and return of the PI Oversight form/UK Regulation Compliance form

(PART 2) to the CI/Sponsor. Each PI must sign off the report from their site. The PI is responsible for ensuring that their site maintains the PI Oversight form/UK Regulation Compliance form (PART 2) at the frequency stated in the UCL JRO Oversight/ Monitoring Plan. The PI must also ensure that all outstanding actions documented in the Monitoring Visit reports are completed.

Site Monitor: delegated individual(s) from the trial's team on site, responsible for completing the PI Oversight form/UK Regulation Compliance form (PART 2) and returning the form to the sponsor or CI as per the UCL JRO Oversight/ Monitoring Plan for review. The Site Monitor must then address any queries raised during the review process and ensure that the final version has been signed and documented in the ISF/TMF as appropriate.

Compliance Oversight Advisor (COA): on behalf of the sponsor, will review the PI Oversight form/UK Regulation Compliance form (PART 2) returned from the sites at the frequency detailed in the UCL JRO Oversight/ Monitoring Plan. The COA will review the findings from a site visit by the external Trial Monitor as documented in the MVR and provides guidance for the required outcome. The COA will perform site visits as the Trial Monitor as required. The COA drafts the UCL JRO Oversight/ Monitoring Plan for the Trial in liaison with the SRA for study specific requirements. The COA assesses suitability of external monitors and oversees compliance with the UCL JRO Oversight/ Monitoring Plan.

Trial Monitor: The individual attending site to monitor, as appointed by the Sponsor. The JRO may appoint an external monitor to conduct monitoring activities on behalf of the sponsor.

Sponsor Regulatory Advisor (SRA)/ Regulatory Manager (ATMP)/ Pharmacovigilance Manager: The Sponsor Regulatory Advisor must be notified of all CAPA arising from PI Oversight form/UK Regulation Compliance form (PART 2) review and/ or Monitoring Visit Reports and may be involved in setting corrective and preventative actions for sites.

Quality Assurance Manager / Clinical Trials Operations Manager (CTOM): Reviews the UCL JRO Oversight/ Monitoring Plan. Reviews the findings from a site visit by the Trial Monitor (only if the COA conducts visit) as documented in the MVR and provides guidance for the required outcome. Upon request by the trial monitor/COA/SRA provides guidance on the creation of CAPA(s) from a review of PI Oversight form/UK Regulation Compliance form (PART 2) or MVR as required.

6. PROCEDURE

6.1 Extent and scope of monitoring (UCL JRO Oversight/ Monitoring Plan)

6.1.1 The determination of the extent and nature of monitoring will be based on the risk assessment as per the risk-based strategy (Appendix 1).

6.1.2 The risk assessment and plan for monitoring will be outlined in the UCL JRO Oversight / Monitoring Plan. Monitoring; whether done on-site or centrally; will involve using the applicable template/s. The final UCL JRO Oversight/ Monitoring Plan will be reviewed and authorised by a delegated individual.

6.1.3 Trial oversight will be conducted in the form of on-site monitoring and central oversight, depending on the risk level of the trial.

6.1.4 The oversight strategy may be amended in response to events in the trial e.g. a high level of SAEs/ SUSARs or recruitment. The UCL JRO Oversight / Monitoring Plan is a live document and will be reviewed and if required, updated accordingly.

6.1.5 The COA will be responsible for reviewing overall compliance with the UCL JRO Oversight/ Monitoring Plan in liaison with the SRA/ RM (ATMP), appointed external monitor (if applicable), trial coordinating team (if applicable) and site staff.

6.2 Central Monitoring: Completion and review of UK regulations compliance forms (part 2)

6.2.1 Central monitoring will be completed at the frequency specified in the UCL JRO Oversight/ Monitoring Plan.

6.2.2 It is the CI or PI's responsibility to allocate a '**site monitor**' within their trial team. This task must be appropriately delegated on the 'Staff Signature and Delegation of Tasks log'.

6.2.3 The site monitor must **complete** the PI Oversight form/UK Regulation Compliance form (PART 2) at the frequency determined in the UCL JRO Oversight / Monitoring Plan.

6.2.4 The PI Oversight form/UK Regulation Compliance form (PART 2) must be **reviewed by the PI** at the site.

6.2.5 The site monitor must **submit** the PI Oversight form/UK Regulation Compliance form (PART 2) at the frequency determined in the UCL JRO Oversight / Monitoring Plan to the JRO.

The following documents will also be submitted with the completed Form:

- Subject Screening Log
- Enrolment, withdrawal and Completion Log
- Staff Signature & Delegation of Tasks log
- IMP accountability logs (single blind/ open labelled trials only)
- Log of Deviations/Violations/Potential serious breaches/Serious breaches
- AE/SAE log

In multi-centre trials, the site monitor may submit the completed PI Oversight form/UK Regulation Compliance form (PART 2) to the CI/CI delegate or submit it directly to the COA/delegate. The CI/delegate will review the completed forms submitted to the JRO to maintain oversight and the CI will provide signature on the final copy of the form.

In single-centre trials, the site monitor will submit the completed PI Oversight form/UK Regulation Compliance form (PART 2) directly to the COA/delegate.

6.2.6 The COA/delegate will review the completed PI Oversight form/UK Regulation Compliance form (PART 2) in a timely manner and add comments to the document as necessary.

A review of the sponsor file by the COA/delegate may be conducted prior to reviewing the returned PI Oversight form/UK Regulation Compliance form (PART 2).

Following the review of the PI Oversight form/UK Regulation Compliance form (PART 2), the COA/delegate should return the form with any applicable comments to the site. Appendix 2 may be used (but not mandatory) as the cover email for return of the PI Oversight form/UK Regulation Compliance form (PART 2) to site.

6.2.7 The CI/PI must **follow the sign off procedure** in the PI Oversight form/UK Regulation Compliance form (PART 2) following satisfactory review by the JRO. Any missing documentation highlighted from PI Oversight form/UK Regulation Compliance form (PART 2) review must be submitted to the JRO as requested.

6.2.8 A JRO representative may go to the site to train the site monitor and PI/CI on completion of the PI Oversight form/UK Regulation Compliance form (PART 2). Any training provided to site team should be documented. In cases where the site has not returned the PI Oversight form/UK Regulation Compliance form (PART 2), a site visit may be arranged in lieu of the form and the site reminded that the PI Oversight form/UK Regulation Compliance form (PART 2) must be returned as per the next submission date to the JRO.

6.2.9 On completion of the review process; a signed and completed copy of the PI Oversight form/UK Regulation Compliance form (PART 2) must be filed in the sponsor file, TMF and ISF (for multicentre trials).

6.3 On-site monitoring:

6.3.1 On site monitoring visits will be conducted at the frequency determined in the UCL JRO Oversight/ Monitoring Plan by an individual appointed by the Sponsor. The Trial Monitor must be appropriately trained, as detailed in the UCL JRO Oversight/ Monitoring Plan.

6.3.2 Planning the visit:

- The Trial Monitor should request dates from site for a monitoring visit and communicate the aims and requirements for the monitoring visit.
- Prior to the visit, the Trial Monitor may conduct a sponsor file review and document the review. If a full sponsor file review is not conducted, the Trial Monitor must ensure they are familiar with the essential documents for the trial.
- The Trial Monitor must also be familiar with all study specific documents such as, but not limited to, the protocol, ICF, PIS, questionnaires, safety reporting procedures and monitoring plan.
- The Trial Monitor will contact the SRA / RM (ATMPs) or COA (if external monitor is used) for recent updates to the trial such as amendments.
- Where applicable, the Trial Monitor must review previous monitoring visit reports to identify any findings that are pending to be resolved or verified during the planned visit.

6.3.3 Each on site monitoring visit will be conducted as detailed in the UCL JRO Oversight/ Monitoring Plan. This will include review of TMF/ ISF, completed trial documents (e.g. Informed Consent forms and CRFs), Source Data and IMP management for the trial.

6.3.4 Documenting conduct of the visit

- The Trial Monitor must sign the Trial Monitoring Visit Log at every visit.
- The Trial Monitor should leave original Monitoring Discrepancy Forms on site and copies should be taken for sponsor records.
- The MVR must be completed after the visit and reviewed as detailed in the UCL JRO Oversight/ Monitoring Plan.
- The completed signed Monitoring Visit Report must be sent to the PI/ CI for filing in the TMF/ISF with any appropriate follow up communication (e.g. e-mail of outstanding items). A copy of the completed, signed MVR should be retained in the sponsor file. Where the ISF / TMF are not the same files (i.e. in multicentre trials), a copy must be filed in the TMF and in the ISF.

7. REFERENCES

The Medicines for Human Use (Clinical Trials) Regulations SI 2004/1031 and as amended

EUCTD 2001/20/EC and GCP Directive 2005/28/EC

MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

ICH GCP: Note for Guidance CPMP/ICH/135/95.

8. APPENDICES:

Appendix 1

Trial Risk-Based Monitoring Strategy

Risk-based monitoring strategy level	Typical phase	Monitoring requirements	Source Data Verification (SDV)*
Risk Level A (**No higher** than the risk of standard medical care)	Phase IV	PI Oversight form/UK Regulation Compliance form (PART 2): Site strongly advised to update every two months and discuss relevant items at site team meetings. SDV by delegated Site monitor Send form to JRO - once a year Site Visit by COA or appointed Trial Monitor (CI site only for multisite trial): once /year (if deemed necessary from the review of the PI Oversight form/UK Regulation Compliance form (Part 2)	25% data 100% consent form review
Risk Level B (**Somewhat higher** than the risk of standard medical care)	Phase III	PI Oversight form/UK Regulation Compliance form (PART 2): Site strongly advised to update every two months and discuss relevant items at site team meetings. SDV by delegated site monitor (sample reviewed at site visit by JRO if required) Send form to JRO - every 6 months Site Visit by COA or appointed Trial Monitor (CI site only if multisite trial): once / year (if deemed necessary from the review of the PI Oversight form/UK Regulation Compliance form (Part 2))	25-50% data 100% consent form review
Risk Level B (**Somewhat higher** than the risk of standard medical care)	Phase IIb	PI Oversight form/UK Regulation Compliance Form (Part 2): Site strongly advised to update every two months and discuss relevant items at site team meetings. SDV by delegated site monitor (sample reviewed at site visit by JRO if required) Send form to JRO - every 6 months Site Visit by COA or appointed Trial Monitor: two / year	50% data 100% consent form review

Risk Level C (**Markedly higher** risk than the risk of standard medical care)	Phase IIa	COA or appointed Trial monitor to conduct site visits SDV by trial monitor PI Oversight form/UK compliance Form (Part 2) does not apply	50-100% data 100% consent form review
Risk Level C (**Markedly higher** than the risk of Standard Medical care)	Phase I	COA or appointed Trial monitor to conduct site visits SDV by trial monitor PI Oversight form/UK compliance Form (Part 2) does not apply	100% data 100% consent form review

*SDV levels may be adjusted if deemed appropriate and justified in the UCL JRO Oversight/ Monitoring Plan. Particular data points such as safety and end point data may be focussed on.

Appendix 2

JRO PI Oversight form/UK Regulation Compliance form (PART 2) Template Email

This can be used to send the JRO reviewed PI Oversight form/UK Regulation Compliance form (PART 2) back to site

Subject: Review of the PI Oversight form/UK Regulation Compliance form (PART 2)

Sponsor Protocol number: XX/XXXX

Please acknowledge receipt of this email.

Many thanks for returning the completed PI Oversight form/UK Regulation Compliance form (PART 2) and supporting documents to the JRO. Having had the opportunity to review the form, please find attached our comments. Please provide a response to all necessary comments within the document.

Please can I request that any points requiring action are resolved by *(insert timeline),* where feasible.

A list of the Corrective and Preventative Actions (CAPA) actions is detailed in the form *on page x*. The actions should be addressed, with the corrective and any preventative action undertaken at site, and timelines detailed in the table accordingly.

Once the actions have been undertaken and all comments resolved, please ensure the finalised form has been signed off by the required personnel at your site and forward me a copy by email for JRO signature. The JRO will retain a copy and I will return the completed form with signature to you.

Finally, may I remind you / delegated site monitor to continue to update this form every two months, saving a copy electronically at each review period. The form only needs to be sent to the JRO for review every *insert frequency here*.

Attachments as listed:

Kind Regards,

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

1	PI Oversight form/UK Regulation Compliance form (Part 2)
2	UCL JRO Oversight / Monitoring Plan
3	Review of Informed Consent Forms (ICFs)
4	Trial Monitoring Visit log
5	JRO Monitoring Visit Report
6	Monitoring Discrepancy Form
Appendix 1: Trial Risk-Based Monitoring Strategy	
Appendix 2: JRO PI Oversight form/UK Regulation Compliance form (PART 2)Template Email	

10. SOP DISSEMINATION & TRAINING

SOPs relevant to the JRO only, will be distributed to the concerned JRO staff, by the named author/delegate under section 11.0 of the SOP. Staff involved by the SOP will sign the SOP training log (Section 12. SOP TRAINING LOG) which is part of each SOP. In addition, each staff has an 'Individual staff SOP training log' and will need to update it once trained on the SOP.

In some instances, the SOP will be basic and the training will constitute of the person reading the SOP and asking specific questions to the author of the SOP. In some instances, the staff member given training will carry out the procedure under supervision of the author of the SOP or under supervision of a staff member who has been trained. Both trainee and trainer will need to sign and date the 'SOP training log' in section 12 of each SOP held by the QA Manager and the 'Individual staff SOP training log'.

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.

Brand new SOPs relevant to 'JRO staff and investigators' or investigators only will be emailed to the investigators and their research team by the lead Trial Co-ordinator. The investigators will be requested to read the new SOP and email back to acknowledge receipt and understanding of the new SOP. The email sent to the investigators and their email acknowledging receipt and understanding of the SOP should be printed out and filed in the JRO SOP folder.

11. SIGNATURE PAGE

Author and Job Title:	Michelle Barber, Compliance Oversight Advisor
Signature:	Michelle Barber Digitally signed by Michelle Barber Date: 2019.06.12 09:13:28 +01'00'
Date:	12/06/19
Authorised by: Name and Job Title	Helen Cadiou, Head of QA
Signature:	Helen Cadiou Digitally signed by Helen Cadiou DN: cn=Helen Cadiou, o, ou, email=h.cadiou@ucl.ac.uk, c=US Date: 2019.06.12 11:08:08 +01'00'
Date:	12/06/19

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							
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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**
14							
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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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