Standard Operating Procedure for Oversight and Monitoring of UCL Sponsored CTIMPs

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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	
JRO/SPON/S19/07	23/10/22	• Added process details for remote monitoring • Administrative corrections and process clarifications	Joanna Saville

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
EHR	Electronic Health Records
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
JRO	UCL Joint Research Office https://www.ucl.ac.uk/joint-research-office/
MHRA	Medicines and Healthcare Products Regulatory Agency
MVR	Monitoring Visit Report
PI	Principal Investigator
QC	Quality Control
REC	Research Ethics Committee
SDR	Source Data Review
SDV	Source Data Verification
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. The monitoring referenced in this SOP can be on-site or remote.

Please check that you are reading the latest version of this SOP: https://www.ucl.ac.uk/joint-research-office/sops-and-templates

2. UCLH/UCL JOINT RESEARCH OFFICE POLICY

All SOPs produced from the Joint Research Office (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. For convenience, this document will use the term 'Regulations' to cover the requirements of the UK SI legislation.

In addition, as UCL sponsors trials with EU and Northern Ireland sites, the SOPs are written to comply with EU Clinical Trials Regulation No. 536/2014.

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/remote monitoring is conducted. For lower-risk trials, on-site/remote monitoring is less frequent, though the Sponsor has developed the PI Oversight form/UK Regulation Compliance form (PART 2) to assist CI/PIs to actively maintain and demonstrate oversight of the trial during its conduct phase. Monitoring can include reviewing medical records, CRFs, and completing source data verification (SDV). SDV should be completed in accordance with Appendix 1. SDV may be completed using the Monitoring Discrepancy Form and Site Data Verification Tracker Form.

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) and on-site/remote monitoring visits. 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/remote 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. Monitoring can occur with a centralised approach to monitoring activities via completion of the PI Oversight form/UK Regulation Compliance form (PART 2) by the site team, on-site or remote monitoring visits by a monitor.

Remote Monitoring: Is the remote direct access to Electronic Health Records (EHR) by Sponsor Monitors (in clinical trials). Remote direct access to the medical/health records of clinical trial participants allows source data review (SDR) and SDV to occur without the Monitor having to visit the investigator site/institution.

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): If the PI Oversight form/UK Regulation Compliance form (PART 2) is applicable, the CI is to ensure that this form 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 ensure all outstanding actions documented in the Monitoring Visit reports (MVRs) for their site (as PI) are completed and help where needed with closing other sites MVR actions. The CI should also review and sign the UCL JRO Oversight/Monitoring Plan if possible.

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 MVRs are completed.

Site Team Monitor: delegated individual(s) from the trial's team on site, responsible for completing the SDV, 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 Team 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 Sponsor Monitor as documented in the MVR and provides guidance for the required outcome. The COA will perform site visits as the Sponsor Monitor as required. The COA drafts the UCL JRO Oversight/Monitoring Plan for the Trial in liaison with the SRA/ RM (ATIMP) for study specific requirements. The COA assesses suitability of external monitors and oversees compliance with the UCL JRO Oversight/ Monitoring Plan.

Sponsor Monitor: The individual attending on-site or obtaining remote access to the EHR and electronic CRF to monitor, as appointed by the Sponsor. The JRO may appoint an external monitor to conduct monitoring activities on behalf of the sponsor. The Co-Monitoring Oversight Visit Report template may be used to assist with ensuring consistency with monitoring.

Sponsor Regulatory Advisor (SRA) / **Regulatory Manager (ATMP):** The Sponsor Regulatory Advisor/ Regulatory Manager ATMP must be notified of all CAPA arising from PI Oversight form/UK Regulation Compliance form (PART 2), reviews UCL JRO Oversight/Monitoring Plan and may be involved in setting CAPAs for sites.

Pharmacovigilance Manager (PVG Manager): Reviews UCL JRO Oversight/Monitoring Plan to ensure it aligns with the trial safety reporting processes and includes monitoring of any important safety endpoints.

Head of Quality Assurance / Clinical Trials Operations Manager (CTOM): Reviews and signs the UCL JRO Oversight/Monitoring Plan. Reviews the findings from a site visit by the Sponsor Monitor (only if the COA conducts visit) as documented in the MVR and provides guidance for the required outcome. Upon request by the Sponsor 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 Trial Risk-Based Monitoring Strategy (Appendix 1), and any specific risk areas identified in the Full Risk Assessment completed for the trial (refer to SPON/07 SOP for granting UCL sponsorship). The risks identified in the Full Risk Assessment are to be reviewed by the COA and should feed into the UCL JRO Oversight/Monitoring Plan for the trial.

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, remotely or centrally; will involve using the applicable template(s). The final UCL JRO Oversight/Monitoring Plan will be reviewed and authorised by the COA, Sponsor Monitor (if applicable), the Head of Quality Assurance and the trial CI (if possible).

6.1.3 The oversight strategy may be amended in response to events in the trial e.g. a high level of SAEs/SUSARs or recruitment, or other events captured in the Full Risk Assessment. If the Full Risk Assessment is updated, then the update should be communicated to the COA and the COA should check if the UCL JRO Oversight/Monitoring plan needs to be updated.

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

6.1.5 When a CTU is delegated to run the trial, the CTU will manage the monitoring completely and the JRO will not be involved in the monitoring.

6.2 Source Document List

6.2.1 Source documents are original documents, data or records which are created during trial and are essential documents which need to be signed and dated in accordance to regulatory and GCP guidelines. The source documents should be listed in the Source Document List template which should be completed prior to site initiation. This template is completed and signed by the COA and the PI together.

6.3 Central Monitoring: Completion and review of UK regulations compliance forms (PART 2) (if applicable)

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

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

6.3.3 The Site Team Monitor is advised to complete the PI Oversight form/UK Regulation Compliance form (PART 2) every 2 months to demonstrate ongoing PI oversight of the trial.

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

6.3.5 The Site Team 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/Urgent Safety Measures

In multi-centre trials, the Site Team 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 Team Monitor will submit the completed PI Oversight form/UK Regulation Compliance form (PART 2) directly to the COA/delegate.

6.3.6 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 monitoring section 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). A review of the monitoring section of the Sponsor file should be completed around once a year.

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.

6.3.7 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.

6.3.8 The COA or delegate may train the Site Team Monitor and PI/CI on completion of the PI Oversight form/UK Regulation Compliance form (PART 2) remotely or on-site. 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.

6.3.9 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 and ISF.

6.4 On-site monitoring:

6.4.1 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 Sponsor Monitor must be appropriately trained, as detailed in the UCL JRO Oversight/Monitoring Plan.

6.4.2 Planning the visit:

- The Sponsor Monitor should request dates from site for a monitoring visit and communicate the aims and requirements for the monitoring visit.
- The Sponsor 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 UCL JRO Oversight/Monitoring Plan.
- The Sponsor 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 Sponsor Monitor must review previous MVRs to identify any findings that are pending to be resolved or verified during the planned visit.

6.4.3 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. ICFs and CRFs), Source Data and IMP management for the trial.

6.4.4 Documenting conduct of the visit

- The Sponsor Monitor must sign the Sponsor Monitoring Visit Log at every visit.
- The Sponsor Monitor should record the actions for the visit in the Outstanding Action Log or within their MVR. The actions should be shared with the site and the Sponsor and filed in the ISF and Sponsor file.
- The MVR must be completed after the visit and reviewed as detailed in the UCL JRO Oversight/Monitoring Plan.
- The completed and signed MVR must be sent to the PI/CI for filing in the ISF with any appropriate follow up communication (e.g. e-mail of outstanding items). A copy of the completed and signed MVR should be retained in the Sponsor file.
- The ICF Review Form can be used to document the review of the completed ICFs.

6.5 Remote Monitoring:

6.5.1 The applicable processes from section 6.4 should be followed. The Sponsor Monitor should set up a meeting with the Trial team to discuss how the Sponsor Monitor can access the essential documents and the necessary systems (e.g. Electronic Medical Records, eCRF etc). The Sponsor Monitor, using e-signature or wet ink, should sign the Monitoring Visit Log. This should be shared with the Site and the Sponsor for filing in the ISF and Sponsor File respectively. As with the on-site visits, actions from the visit should be recorded in the Outstanding Action Log or within the MVR and provided to the Site and Sponsor.

If a TMF/ISF review is required, where the TMF/ISF is electronic, read only access will be granted to the Sponsor Monitor in order to complete a review. If there is no electronic TMF/ISF, no review can be completed so an on-site visit should happen if possible.

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.

EU Regulations 536/2014

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 Team Monitor Send form to JRO - once / year Site Visit by COA or appointed Sponsor 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)	10-25% 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 Team Monitor (sample reviewed at site visit by JRO if required) Send form to JRO - every 6 months Site Visit by COA or appointed Sponsor 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 Team Monitor (sample reviewed at site visit by JRO if required) Send form to JRO - every 6 months Site Visit by COA or appointed Sponsor Monitor: two / year	50% data 100% consent form review
Risk Level C (**Markedly higher** risk than the risk	Phase IIa	COA or appointed Sponsor monitor to conduct site visits SDV by Sponsor Monitor	50-100% data

Risk-based monitoring strategy level	Typical phase	Monitoring requirements	Source Data Verification (SDV)*
of standard medical care)		PI Oversight form/UK compliance Form (PART 2) does not apply	100% consent form review
Risk Level C (**Markedly higher** than the risk of Standard Medical care)	Phase I	COA or appointed Sponsor monitor to conduct site visits SDV by Sponsor 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.

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	ICF Review Form
4	Sponsor Monitoring Visit Log
5	JRO Monitoring Visit Report
6	Outstanding Action Log
7	Pharmacy Monitoring Visit Report
8	External Monitor Transfer of Trial Responsibilities
9	Source Document List
10	Monitoring Discrepancy Form
11	Site Data Verification Tracker
12	Co-Monitoring Oversight Visit Report
13	SPON/S07 SOP for granting UCL sponsorship
Appendix 1: Trial Risk-Based Monitoring Strategy	

10. SOP DISSEMINATION & TRAINING

SOPs will be distributed to the concerned staff. Staff concerned by the SOP will sign the SOP training log (12. SOP TRAINING LOG) which is part of each SOP.
In some instances, the SOP or the changes to the SOP will be basic. 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.

SOPs relevant to “JRO staff and investigators” or investigators only will be provided to the investigators at the time of the trial initiation. The investigator will sign section 12 of the SOP, the “SOP training log”.

The SOPs and relevant templates and logs will be available on the JRO website shortly after having been released.

11. SIGNATURE PAGE

Author and Job Title:	Joanna Saville, Compliance Oversight Advisor
Signature:	DocuSigned by: Joanna Saville 3B5B31E4F5C7472...
Date:	23/09/22
Authorised by: Name and Job Title	Helen Cadiou, Head of QA
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	23/09/22

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**
1							
2							
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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**
6							
7							
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11							

	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**
12							
13							
14							
15							
16							
17							

	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**
18							
19							
20							
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24							