UNIVERSITY OF SUSSEX

Standard Operating Procedures for Monitoring CTIMPs

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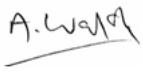
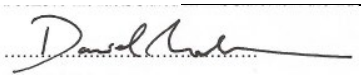
Author: Antony Walsh **Designation:** RES Research Governance Officer	*Signature* 	*Date* 26 May 2021
Authorised by: Dr Daniel Michelson **Designation:** SSC Chair		11 June 2021

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Acknowledgement, BSUH, BS CTU

[1] http://www.sussex.ac.uk/staff/research/governance

1. Purpose & Scope

1.1 The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union (EU). It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document[2].

1.2 This SOP describes the processes that are involved for monitoring of a Clinical Trial of an Investigational or Medicinal Product (CTIMP).

1.3 The scope of the document is for all schools at the University of Sussex (US), all members of staff with substantive employment and students registered at the University (including Brighton and Sussex Medical School (BSMS)) undertaking CTIMPs. The scope of the document includes anyone undertaking activities for a Clinical Trial on behalf of the University.

2. Introduction

2.1 The purpose of monitoring CTIMPs is to ensure that they are conducted in accordance with ICH Good Clinical Practice (GCP) guidelines, the relevant regulations, the trial protocol and other associated procedures.

2.2 Monitoring should also verify that the research site remains adequate, the team are appropriately trained and supported, the reported trial data are accurate, complete and verifiable against the source data and that processes are followed and activities consistently documented as evidence of compliance.

2.3 The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031) and subsequent amendments define monitoring as:
"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol and any amendments, written procedures, GCP, and the applicable regulatory requirement(s).

2.4 Section 5.18 of ICH GCP describes the purpose of trial monitoring as verifying that:
(a) The rights and well-being of human subjects are protected.
(b) The reported trial data are accurate, complete, and verifiable from source documents.
(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

2.5 Sponsor oversight and monitoring of studies will be achieved through both central and study specific monitoring activities. For CTIMPs the study oversight and monitoring arrangements will be defined in the protocol and monitoring plan and will include the establishment of an appropriate study

management and oversight group(s) or committee(s). This will be managed through the CTU supporting the study.

3. Responsibilities

Sponsor

3.1 It is the responsibility of the Sponsor to ensure that trials are adequately monitored.

3.2 The Sponsor will usually allocate a Trial Manager (TM) or Trial Monitor (tm) to monitor a certain research project unless one has been appointed by a CTU. The Trial Manager/Monitor should be adequately trained and qualified.

3.3 The Sponsor will review sponsor summaries from monitoring visits at regular meetings of the Sponsorship Sub-Committee (SSC) and follow up any actions required.

3.4 The Sponsor will audit monitoring activities from time to time and will request access to monitoring visit reports and study specific non-compliance logs.

3.5 The Sponsor will review any urgent issues identified during monitoring activities and may meet with key study personnel to resolve the issue.

Chief Investigator

3.6 The Chief Investigator (CI) is responsible for establishing appropriate study management and oversight groups appropriate to the trial.

3.7 The study management and oversight arrangements for trials should be defined in the protocol and detailed in the study-specific monitoring plan before site activation. For US sponsored studies, a Trial Management Group (TMG) may be sufficient and should consist of at least the CI/PI and Trial Manager. For larger more complex and higher risk studies, there may also be an independent Data Monitoring Committee (DMC). For CTIMPs a Trial Steering Committee (TSC) will be required and this may be as well as a Trial Management Group.

3.8 The decision for oversight arrangement will be made on a case by case basis and agreed by the sponsor before study initiation.

3.9 Trial Management and oversite committee meeting minutes will be filed in the Trial Master File (TMF) and Investigator Site File (ISF) and a summary of monitoring activities provided to SSC on an annual basis.

Trial Manager (TM)

3.10 The TM/tm is responsible for following SOPRG005A, 'Monitoring CTIMPs for US sponsored studies, and the relevant CTU SOP.

3.11 The TM/tm must schedule and conduct monitoring visits for the CTIMP that has been allocated to them by US in line with the monitoring plan.

3.12 The TM/tm is responsible for writing the monitoring visit report and sponsor summary as well as escalating to the Sponsor any urgent issues identified as soon as possible.

3.13 When applicable, a study specific non-compliance log should also be maintained by the TM.

3.14 The TM is also responsible for filing the report and any relevant correspondence in the TMF.

US Research Governance Officer (RGO), CTU Operational Manager (OM)

3.15 In CTIMPs, the TM/tm is responsible for undertaking monitoring risk assessments, creating monitoring plans and developing trial specific monitoring tools for each clinical trial. The OM and US RGO are responsible for reviewing these documents.

3.16 The OM is responsible for reviewing and approving the monitoring visit report for consistency and compliance before the report is sent to the site. When appropriate, the RGO will report significant findings to the SSC.

Principal Investigator (PI)

3.17 The PI is responsible for ensuring that their team is present at the site initiation visit, that the TM/tm has access to the necessary documentation at the site and that the appropriate staff are available to participate at subsequent monitoring visits in line with the monitoring plan. They are also responsible for signing off protocol deviations and ensuring that the appropriate corrective and preventative action is taken and that queries raised at the monitoring visit are responded to in a timely manner.

4. Procedure

Prior to Trial Opening

4.1 Prior to the trial commencing, a monitoring risk assessment will be performed and documented for all CTIMPs sponsored by US. This will aim to identify risks associated with the trial and any mitigation that can be implemented to reduce the risks identified.

4.2 A monitoring plan will be written by the TM/tm and reviewed by the RGO, and Chief Investigator (CI). The monitoring plan will specify the type of monitoring to be performed, the frequency of the monitoring and how often different monitoring activities should be performed after considering the monitoring risk assessment for the trial. This will be based on the outcomes of the trial, the design, endpoints, complexity, size, experience of research teams and risks posed by the Investigational Medicinal Product (IMP) and other trial related activities.

4.3 Trial specific monitoring tools such as checklists and source data specification lists will be created by the TM/tm and approved by the RGO prior to the start of the trial, in order to assist the TM/tm with the monitoring. These documents should be fully executed prior toe site activation. The monitoring plan should be signed off by the PI at the site initiation visit (SIV).

Preparation for a Monitoring Visit

4.4 The first monitoring visit will be conducted in line with the timelines agreed in the monitoring plan once the study has started recruiting. The TM/tm, who will be thoroughly familiar with the protocol and all other written information for the trial, will confirm the date via email with the research site and ensure that all those required to be present are available. Availability of other departments

such as pharmacy, laboratories, imaging and other specialist units should be considered when making arrangements for the monitoring visit. The Source Data Specification list can be referred to prior to the visit to ensure the TM/tm has access to all source data at the time of the visit.

4.5 If there have been previous monitoring visits, then the monitoring visit reports should be reviewed along with any data queries for outstanding issues. Any new documents that require signing by the site should be prepared so that the relevant signatures can be obtained.

4.6 The TM/tm should request that the site make every effort to complete paper or electronic CRFs and answer any outstanding queries prior to the monitoring visit.

Onsite Monitoring Visit

4.7 An on-site monitoring visit is where the TM/tm visits the research site. Examples of on-site monitoring activities include:

4.7 a General

- Review of ICFs (informed consent forms) for every patient before patient data is reviewed
- Review of the consent process checking that it is in line with any applicable SOPs
- Checking that dates of signatures do not precede trial procedures
- Checking that eligibility of participants has been confirmed
- Checking other trial processes are documented in the participant's medical records
- Ensuring correct versions of documents are being used
- Checking that amendment documentation is in place, that sites have implemented the changes outlined in recently approved amendments and re-consenting has occurred when required
- Review of CRFs and source data verification
- Generation and resolution of data queries on the eCRF system or if paper CRF, data clarification forms (DCFs). Queries should be resolved at the time with research site staff if at all possible
- SAE reconciliation with SAE reports, source data and CRF/eCRF entry
- Checking that the SAE process has been followed as per SOPRG21- Adverse Events in CTIMPs
- Ensuring the PI has reviewed all relevant safety information for the trial
- Ensuring the PI has reviewed any out of range findings (e.g. lab tests, blood pressure etc.)
- Conducting appropriate training activities; including the protocol, SOPs and eCRF/CRF training
- Review of the Investigator Site File (ISF)
- Ensuring the delegation log is updated with any changes in the research team
- Ensuring CVs for everyone on the delegation log are signed within the last year (unless otherwise specified for certain studies)
- Ensuring that GCP certificates for everyone on the delegation log are dated within the last 2 years and documentation of trial specific training is available for each staff member on the delegation log for the trial unless agreed otherwise by the Sponsor and the CI.
- Checking calibration of equipment used for the trial
- Checking hospital laboratory normal ranges and certification of accreditation
- Discuss any protocol deviations, ensure they are logged on a Protocol Deviation Log, noted in the CRF and any corrective or preventative actions are agreed as appropriate
- Reporting potential serious breaches to the Sponsor immediately as per SOPRG03 Notification of Serious Breach of Good Clinical Practice or the Trial Protocol

- Ensuring the monitoring visit log is signed by both the TM/tmand a member of the research team at the site
- Reviewing emergency 24-hour contact details for any changes

4.7b Biological Samples

- Checking the labelling, collection and storage of biological samples is in line with the lab manual or trial protocol
- Reviewing the laboratory trial file
- Reviewing shipment of samples where necessary
- Checking that there is adequate stock of trial supplies e.g. blood collection tubes

4.7c Pharmacy

- Verifying drug accountability
- Ensuring storage facilities remain adequate and temperature logs and calibration certificates are reviewed and copies are taken for the TMF
- Ensuring chain of custody from receipt, use, return and destruction of IMP (investigation medicinal product)
- Ensuring sufficient supply of IMP
- Checking expiry dates
- Reviewing the trial pharmacy file
- Ensuring that the monitoring visit log in the pharmacy file is signed by both the TM/tm and a member of the pharmacy team

After the Monitoring Visit

4.8 Immediate actions, such as escalating a potential serious breach to the Sponsor, should be followed up straight away, at least within one working day of the monitoring visit.

4.9 A monitoring visit report should be written by the TM/tm and sent to the OM within 5 working days, so that it can be reviewed and then sent to the research team, copying in the RGO, within 10 working days of the visit. The Monitoring Visit Report template should be used, which includes a summary of what was reviewed, significant findings, deviations, deficiencies and actions taken or to be taken to ensure compliance. The research team should file a copy in the ISF. The TM should file a copy in the TMF.

4.10 Any copies of documents taken from the research site should be noted in the monitoring visit report and then filed appropriately in the TMF at the coordinating centre if applicable. These should include:

- Copy of the delegation log
- Copies of GCP certificates and CVs of those on the delegation log
- Copies of training logs for study specific training
- Copies of training records for sponsor SOPs

- Copies of local R&D approval letters for amendments

4.11 Any actions requiring follow up that are not addressed within the timelines agreed or by the next monitoring visit, will be discussed with the research team. If the research team still fail to complete the actions then this issue should be escalated to the Sponsor.

4.12 The RGO will present a summary of the findings from monitoring visits to the SSC, who meet at least quarterly.

Central Monitoring

4.13 Central monitoring is when monitoring activities are performed remotely from the coordinating centre. With low risk studies across wide geographical areas there may be more desire to monitor remotely as much as possible This could include but is not limited to:

- monitoring recruitment rates across sites
- reviewing missing/incorrect data on a central database
- monitoring the number of serious adverse events reported across sites.
- receipt and review of consent forms (if permitted and consented to)
- reviewing eligibility
- checking CVs and GCP training
- reviewing drug accountability

4.14 If central monitoring is to be used as a method for monitoring the trial then triggers for further action should be specified in the monitoring plan. Triggers may include:

- Significant differences in recruitment numbers at sites that have similar recruitment potential.
- Significant differences in the numbers or types of serious adverse events reported at different sites.
- Lack of data entry in the database despite participants being recruited.
- Unusual patterns of data identified by statistical monitoring.

4.15 A central monitoring report should be produced as evidence of the monitoring being conducted in line with the frequency specified in the monitoring plan. Any significant findings or triggers identified should be actioned immediately by the TM. The RGO should be notified and appropriate action agreed and implemented e.g. on-site visit to be arranged or further training required at the research site.

4.16 Significant findings from central monitoring will be communicated and discussed with the research site when applicable. The central monitoring report and any associated correspondence will be filed in the TMF and ISF at the research site.

5. Training

5.1 This is a ‘read and understand’ SOP. Please note that the R&D department discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the University website.

6. Abbreviations

AE	Adverse Event
BSCTU	Brighton and Sussex Clinical Trials Unit
BSMS	Brighton and Sussex Medical School
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF (eCRF)	Case Report Form (electronic Case Report Form)
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
HSC	Health and Social Care
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
IVD	In Vitro Diagnostic
JCRO	Joint Clinical Research Office
LIP	Local Information Pack
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
OM	Operational Manager
PI	Principal Investigator
PAF	Portfolio Application Form
PPI	Patient and Public Involvement
PVG	Pharmacovigilance Manager
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RGO	Research Governance Officer

RM(ATIMPS)	Regulatory Manager for ATIMPS
RM(P)	Regulatory Manager (Pharmaceuticals)
SAE	Serious Adverse Event
SDF	Source Data Verification
SI	Statutory Instrument
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SSC	Sponsorship Sub-Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
tm	Trial Monitor
TMF	Trial Master File
TMG	Trial Management Group
TM	Trial Manager
tm	Trial Monitor
TSC	Trial Steering Committee
US	University of Sussex

7. Cross Referenced SOPs

SOPRG03 Notification of Serious Breach of Good Clinical Practice or the Trial Protocol
SOPRG21 Adverse Events in CTIMPs
SOPRG09 Procedures for Close out of a CTIMP
SOPR6016 Amendments, Urgent Safety Measures and Temporary Halt of Trial

8. References

Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, SI 1031
http://www.legislation.gov.uk/uksi/2004/1031/contents/made

ICH Good Clinical Practice Section 1.38 and 5.18
https://www.ich.org/page/efficacy-guidelines

Good Clinical Practice Guide MHRA/ Stationery Office (Great Britain), London: 2012

ON-SITE MONITORING REPORT

(To be adapted on a trial by trial basis)

Study Title: [Full study title]	
EudraCT Number:	
IRAS Number:	
Name and Number of site:	
PI Name:	
Reason for visit:	
Date of visit:	
Preparation for visit	
Visit correspondence (date and to whom)	
Has version control list been sent ahead of visit and any documents identified as missing now been sent?	
Protocol version number current at visit	
Number of patients randomised (and date)	
Calculate 20% of total patients and ask non-team member to randomly select corresponding number of patient records. State patient IDs to be checked at visit	
Have 100% of completed ICFs been checked via central monitoring prior to visit?	
Is database and database checks up to date? If not, comment on impact for on-site visit	

During the visit	
Members of site staff present (list names and roles)	
Member(s) of CTU/ member (s) of REIGO conducting visit	
Number of patients randomised to visit date	
Number of patients screened	
Number of patients who have reached week (n) (end of main study) visit	
Number of SAEs at this site to date (total and as% of number recruited)	

	ITEM MONITORED		YES	NO	N/A	COMMENTS (if no is answered, comment)
	1 Review of ISF					
	The following documents should be present and current version:					
	Protocol	[version no.]	☐	☐	☐	
	Patient Info Sheet (PIS)		☐	☐	☐	
	Patient ICF		☐	☐	☐	
	General comments on ISF (if any)					

2.	**Informed consent and participant status**

	Item Monitored	**YES**	**NO**	**N/A**	**COMMENTS (if no is answered, comment)**
	Are ICFs present for legal rep/patient and carer for all randomised dyads?				
	Capacity form filed for each participant?				
	Is the site maintaining logs of screened/enrolled participants?				
	If medical records are available for review, confirm that it is noted that patients are enrolled in the trial. If records are not reviewed ask staff about this process.				
	How many participants have withdrawn/stopped treatment or been lost to follow up? Are these CRFs available for review?				
	General comments on informed consent and participant status (if any):				

3.	**Protocol adherence and medical records review**

	Item Monitored	**YES**	**NO**	**N/A**	**COMMENTS (if no is answered, comment)**
	Evidence being recorded that participants meet eligibility criteria?	☐	☐	☐	
	Are medical notes available for review? Was SDV from medical notes carried out?	☐	☐	☐	
	For specified patient records, are blood/ECG records printed, filed and signed by the PI for each relevant patient?	☐	☐	☐	

		Have any protocol deviations been found or recorded in notes?	☐	☐	☐	
		General comments on protocol and medical records review (if any):				
	4.	**CRF review and Source Data Verification (SDF)**				
	Item Monitored		**YES**	**NO**	**N/A**	**COMMENTS (if no is answered, comment)**
	Are CRF pack/patient notes available for every patient randomised to date? Note any numbers that are missing.					
	Have all queries been resolved on database to date?					
	Are all randomisation emails printed and filed in the appropriate place?					
	Is data entry up to date on the database?					
	Are patient notes filed appropriately for each patient?					
	General comments on CRF review and Source Data Verification (SDF)					
	5.	**Pharmacovigilance**				
	Item Monitored		**YES**	**NO**	**N/A**	**COMMENTS (if no is answered, comment)**
	Are SAE reports filed?					
	Are there any outstanding SAE queries to be resolved?					

	Does the information at site match what the CTU holds?				
	From SDV/medical record checks is there any evidence that AEs are underreported or have any new AEs been found?				
	General comments on Pharmacovigilance				
6.	Pharmacy/ IMP				
	Item Monitored	**YES**	**NO**	**N/A**	**COMMENTS (if no is answered, comment)**
	Are tablet counts being recorded on the database?				
	Is there an up to date pharmacy delivery log?				
	Are pharmacy activities clearly separated from site activities and is blinding being maintained?				
	General comments on Pharmacy/ IMP				

Outcomes from visit	
Have there been any major or critical findings?	
Have there been any protocol deviations?	
Are there any other actions required and/or follow ups needed?	
Have all actions from previous visits been closed (if applicable)?	

Comments

Give a brief overview of the meeting and highlight whether there were any particular issues e.g. key member of trio/ team not present, anything raised for discussion that requires further consideration by the CI/NCTU team, or that represents further need to follow up.

Report completed by (TM/tm) :

Name and role *(print):*		Date:
Signature:		

Report reviewed by (CTU Operational Manager)

Name and role *(print):*		Date:
Signature:		

Report reviewed by Chief Investigator

Name *(print):*		Date:
Signature:		

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SPONSOR SECTION

(NOT TO BE INCLUDED IN MAIN REPORT TO SITE)

Issues to be escalated to sponsor	Sponsor review date	Recommended actions / comments from Sponsor

CENTRAL MONITORING REPORT

(To be adapted on a trial by trial basis)

[Short study name]

Study Title: [Full study title]	
Sponsor reference:	**EudraCT Number**:
REC reference:	**IRAS Number:**
Chief Investigator:	
Sponsor:	
Trial Manager:	
Site:	
Principal Investigator:	
Research Nurse: **Data Officer:**	

OVERALL STUDY PROGRESS	
Date Site opened to recruitment/ activated	
Total number of patients screened:	
Total number of patients recruited:	
Number of patients ongoing:	
Number of patients completed:	
Study completion due date:	
Predicted total at study completion based on current recruitment:	
Total number of withdrawals:	
Total number of those withdrawals due to safety:	
Total number of SAEs:	
Total number of SUSARs:	

Date of previous report: DD/MMM/YYYY
Date of current report: DD/MMM/YYYY

ACTIONS OUTSTANDING FROM PREVIOUS MONITORING REPORT

Item	Action and Update	Responsibility	Due date

DATA MANAGER REVIEW (DMR)

Date DMR completed: DD/MMM/YYYY

DMR reviewed by Trial Manager: ☐ Date: DD/MMM/YYYY Not reviewed: ☐

SUMMARY OF SIGNIFICANT FINDINGS / OUTSTANDING ACTIONS from DMR:

ENDPOINTS:

DATA:

PROTOCOL COMPLIANCE:

OTHER:

PROTOCOL DEVIATIONS: Since last monitoring report

DEVIATION NUMBER	SUMMARY	DATE OF DEVIATION	REPORTED BY	DATE REPORTED
Deviation 1:				

Have any of these been escalated to sponsor? Yes ☐ Date: DD/MM/YYYY No ☐

ACTIONS REQUIRED:

CONSENT FORMS:

Number of participants consented since last monitoring report:

SUMMARY OF OUTSTANDING ISSUES REGARDING CONSENT:

ACTION:

SCREENING/ENROLMENT LOG: Since last monitoring report		
Date log received	**Number of people screened / enrolled**	**COMMENTS**
ACTION:		

SCREENING LOG: Since last monitoring report			
Date screening log received	**Number of people screened**	**Number of screen failures**	**Reasons for screen failure**
ACTION:			

DELEGATION LOG:			
Date of most recent delegation log received	**Evidence received of training for any new staff**	**GCP outstanding (signed within 2 years)**	**CV outstanding (signed within 1 year)**
Any issues with staff who received consent or confirmed eligibility?			
ACTION:			

SERIOUS ADVERSE EVENTS:		
SAE number	**Is SAE complete?**	**If No, what is outstanding?**
ACTION:		

IMP MANAGEMENT & PHARMACOVIGILANCE:		
Documents Received	**Date Received**	**Comments**
Temperature logs		

Review of IMP orders		
IMP stock check at site		
General Drug Accountability log		
Patient drug accountability log		
IMP Destruction Log		
ACTION:		
LAB MANAGEMENT:		
DOCUMENT	**DATE RECEIVED**	**COMMENTS**
SAMPLE LOG		
NORMAL LAB RANGES		
TEMPERATURE LOG		
SAMPLE TRANSFER LOG		

LOCALISED DOCUMENTS (VERSION CONTROL)		
Date Current version list (version control) emailed to site	**Date of site response regarding correct use of documents**	**COMMENTS**
DD/MM/YYY	**DD/MM/YYY**	
ACTION:		
EARLY WITHDRAWAL		
Subject ID/initials	**Date of withdrawal**	**Reason for withdrawal**

ACTION:		

ADDITIONAL ACTIONS LOG

Item	Action to be taken	Responsibility	Due date

I certify that the above information has been reviewed and/or verified:

Trial Manager Review	
Name of Trial Manager	
Signature	
Date	

CTU Operational Manager Review	
Name	
Signature	
Date	

PI Review	
Name of PI	
Signature	
Date	

<OPTIONAL – REMOVE OR AMEND AS PER STUDY REQUIREMENTS>

Appendix 1: Patients overview (as of XXXX)

	Date of consent	Study ID	Date recruited	Arm	Last visit entered on MACRO

SPONSOR SECTION

(NOT TO BE INCLUDED IN MAIN REPORT TO SITE)

Issues to be escalated to sponsor	Sponsor review date	Recommended actions / comments from Sponsor

Appendices

SPONSOR SECTION

(NOT TO BE INCLUDED IN MAIN REPORT TO SITE)

Issues to be escalated to sponsor	Sponsor review date	Recommended actions / comments from Sponsor