UNIVERSITY OF LEICESTER

<INSERT SHORT TRIAL TITLE> Monitoring Plan

Site:	
Sponsor Reference Number:	
Full Trial Title:	
Chief Investigator:	
EudraCT Number:	**<delete if N/A>**
IRAS Number:	

The Sponsor risk assessment form and the trial risk based monitoring strategy, appendix 2 to SOP S-1007, will inform the development of the monitoring plan.

The monitoring risk category for this study is **<insert trial Type of Risk and definition>**.

The type of monitoring undertaken, its frequency and the focus of monitoring visits will be determined by the risk rating allocated. All aspects will be undertaken in accordance with the Sponsor Standard Operating Procedures.

The monitoring plan should be used as a guide for monitoring activity and is subject to revision(s) dependent upon on participant enrolment rate, quality issues, site compliance or other trial issues. However, any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring visit report and the plan amended if appropriate. The number and frequency of monitoring visits is subject to change and will be dependent upon the number and type of findings at each visit. The amount of Source Data Verification conducted is also subject to increases or decreases based upon findings and in accordance with the risk-based (adaptive) approach to monitoring.

If the site does not enroll any patients or enrolment is stopped, regular monitoring visits will not be scheduled. If there is an extended gap in trial activities the monitor will ensure that site staff are appropriately trained when trial activities recommence.

1. Frequency of monitoring visits

1.1 Initiation visit

The study team initiation visit took place **<on-site/remotely>** on **<insert date>**, the Pharmacy initiation visit took place **<on-site/remotely>** on **<insert date>**, IMP delivered to the site on on **<insert date>** was checked during the visit.

<insert details regarding additional site initiation activities being conducted by vendor(s) and comments regarding Sponsor oversight of vendor monitoring, if applicable>

1.2 First monitoring visit

The first monitoring visit will take place **<on-site/remotely>** within **<insert details, ensuring that it is specified that a visit takes place before or after randomisation/dosing and checking against the monitoring quote as appropriate>**.

1.3 Interim monitoring visits

Interim monitoring visits will take place **<on-site/remotely> <insert details, ensuring that it is specified that a visit takes place before or after a certain number of participants are recruited/randomisation/dosed and checking against the monitoring quote as appropriate>** in accordance with the rate of recruitment, the amount of data being generated, quality issues, site compliance or other trial issues. Up to **<insert details checking against the monitoring quote as appropriate>** interim monitoring visits will be conducted. Remote monitoring visits may need to be conducted more often but would focus on specific matters/areas so as to not over-burden the research team.

The study database will be monitored periodically to ensure that data transcription from the CRFs is accurate, that data are being entered in a timely manner, that data fields are not left blank without reason and to oversee the number and type of data value overrides/errors. Queries raised through the eCRF system will form part of the monitoring schedule. Drug compliance checks may be performed through the system.

The trial will also be subject to **<insert details checking against the monitoring quote as appropriate>** audit visit**(s)** to be completed by the Sponsor delegate.

Consider the timing of interim monitoring visit(s) for dose escalation studies and/or data monitoring committee review of data.

1.4 Close out visits

A close out visit will be conducted within 3 months of last patient last visit, and prior to database lock

Ensure all aspects of study closure are completed as per Sponsor SOP S-1024.

1.5 Contact with the Principal Investigator

The monitor will meet/have contact with the Principal Investigator and/or delegate at each of the above mentioned visits to discuss study progress and issues. This may become more difficult with remote monitoring visits, but a pragmatic approach will be taken in that issues of concern or urgency or require a medical opinion will be directed to the CI/PI.. All other matters according to a risk-based approach will be dealt with the most appropriate member of staff. The PI will be copied into all monitoring report correspondence.

2. Monitoring

The monitor should complete and sign the Trial Monitoring Visit Log at each visit

2.1 Recruitment

The trial specific recruitment plan and recruitment timeframe was discussed at the site initiation visit.

Recruitment period is anticipated to be approximately **<insert details>**.

<Delete/retain as appropriate> The investigator **may/may not** re-screen a subject who fails screening, up to **<insert details>** more times on different days, assuming the following criteria are met:

- In the investigator's judgement, the subject is now likely to meet all eligibility criteria as the original cause for screen failure is no longer applicable
- The re-screened subject must be re-consented, be issued a new subject number, and have all screening assessments performed again.

2.2 Eligibility

The inclusion and exclusion criteria should be checked in full as per the latest approved protocol.

The monitor will check that each participant meets ALL of the inclusion criteria and NONE of the exclusion criteria against the available information in the participant medical records and documentation to support results, and annotation of the screening/eligibility documentation. The monitor will check for confirmation of eligibility statement from the persons delegated to confirm eligibility. This decision should be clearly documented in the medical notes and signed by the medically qualified doctor making the decision prior to dosing of the subject.

Any deviation identified by the monitor from the inclusion/exclusion criteria must be documented as a protocol breach/deviation.

2.3. Primary/Secondary endpoints

The monitor will check that the data required to achieve the primary and secondary endpoints have been collected in accordance with the latest approved protocol and that all assessments have been conducted correctly. Collected data should be recorded on source worksheet/CRF as per protocol and expectations for source data.

To ensure primary endpoints can be achieved the monitor will establish the following data is collected:

<insert details including the endpoint and the timeframe of the endpoint, for example, X at 24 weeks>

To ensure secondary endpoints can be achieved the monitor will establish the following data is collected:

<insert details including the endpoint and the timeframe of the endpoint, for example, X at 24 weeks>

OR

<Delete/retain as appropriate> There are no secondary endpoints for this protocol only exploratory endpoints therefore unaffected by missing data.

Any missing, spurious or incomplete data will be highlighted within the monitoring report for action. Where there are significant non-compliance or deficiencies within the data these must be highlighted to an appropriate member of the study team during the visit, documented in the monitoring report and followed up by written communication with the Principal and/or Chief Investigator as appropriate. Non-compliance will be escalated as per SOP S-1016 and in the case of a serious breach as per SOP S-1013.

3. Consent

Informed consent is fundamental to research and must have been given prior to ANY study related procedures. The process of obtaining informed consent is per SOP S-1021.

The monitor will ensure that the correct process with regards to the approach, provision of information, timescale for patient review prior to consent is as documented in the Ethics application.

The monitor will check the Informed Consent Form (ICF) and Participant Information Sheet (PIS) for each subject to ensure that:

1) The current, approved version has been used.

2) The original signed copy of the ICF and PIS is placed in the Site File. These must be correctly completed by both the participant and person obtaining the informed consent.

The monitor will check that the process of informed consent has been documented in the participant's medical notes and that this has been dated and signed by the person obtaining the informed consent.

The monitor will check that the person conducting the informed consent procedure is documented as authorised to do so, by review of the Delegation of Authority and Signature log.

The monitor will document non-compliance with the correct consent procedure in the Monitoring Visit Report. Non-compliance will be escalated as per SOP S-1016.

4. Source Data Verification (SDV)

Source Data is comprised of records where subject information is first recorded. It includes, but is not limited to, medical records, lab results, scan results, questionnaires, and where agreed, the CRF or trial worksheets. Where there is a Source Data Agreement (SDA), any items defined as being entered directly into the CRF cannot be verified. The amount of SDV conducted will be compliant with the risk rating allocated at Sponsor review and is subject to increases or decreases based upon monitoring visit findings and in accordance with the risk-based (adaptive) approach to monitoring.

<Amend details in the table below as necessary and in accordance with the SDA, sources of data included as examples>

Amount to be monitored should be as per the Monitoring Strategy Table.

Data/Parameter	Source of Data	Amount to be monitored
Subject ID numbers and initials	Signed Informed Consent Forms, Medical Records, and Screening and Enrolment Logs, eCRF/CRF	
Date of written informed consent	Signed Informed Consent Forms, Medical Records, and Screening and Enrolment Logs, eCRF/CRF	
Eligibility	Medical Records, eCRF/CRF, laboratory results, GP letters	
Subject past medical history, demographic data, con. meds, anthropometrics, vital signs, pregnancy testing	Medical Records and eCRF/CRF/study-specific worksheets, EMR system	
Visit Dates	Medical Records and CRFs/eCRF	
Questionnaires **<list if required>**	Completed questionnaires with participant records/CRFs	
Clinical Laboratory Assessments **<list if required>**	Lab report print outs (assessed and signed by the PI/delegated medic)	
Key efficacy variables		
Primary endpoints (and time points for checking)		
Secondary endpoints (and time points for checking)		
Compliance with dosing regimen	Dosing sheet, IMP/placebo preparation records, patient notes and medical records, study-specific worksheets, EMR system	

Serious Adverse Events and Adverse Events	Medical Notes, CRFs/ study-specific worksheets, Adverse Events Logs (paper and eCRF) and TMF (SAE reports)	
Drug Accountability and Compliance	Pharmacy accountability logs, prescriptions (checking maintenance of the randomisation results) and bottles to be checked, CRF/eCRF will record compliance	

The monitor will discuss any discrepancies, noted in the source documentation versus study data, with the site staff and request that the data be corrected by an authorised person. If data cannot be altered during the monitoring visit, the monitor must ensure that the changes have been made by the next visit to site.

5. Regulatory Compliance

At each visit the monitor will ensure that any amendments have been correctly notified to the appropriate statutory and regulatory bodies and that all necessary approvals are in place.

The monitor will also ensure that all annual reports have been completed and submitted in a timely manner to the correct regulatory bodies.

6. Protocol Breaches and Deviations

Any deviations from planned assessments or procedures, as defined in the study protocol, should be documented. Protocol breaches and deviations must be documented in the monitoring visits report, in the CRF/eCRF (if there is a comments field available) and as a file note as appropriate. This documentation must be filed in the Trial Master File/Investigator Site File.

Protocol breaches and deviations should be logged in a cumulative tracking sheet on an ongoing basis utilising the Sponsor CAPA Template, or the Protocol Deviation Log, respectively. This will aid decision making at the time of data analysis and interpretation, and can help to spot protocol deviation trends. Protocol deviations that recur across different subjects may highlight a particular section of the protocol/a procedure that is causing the site difficulty.

Protocol breaches and deviations should be discussed with this site at the earliest opportunity, to ensure that re-occurrences of the same issue are kept to a minimum, and to discuss whether particular issues highlight a need to revise the study protocol by way of a substantial or non-substantial amendment. Serious breaches of protocol will be reported as per Serious Breach SOP S-1013.

7. Safety Monitoring

Processing and reporting of Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions will be undertaken as per SOP S-1009, the protocol, and as per the Safety Data Exchange Agreement (if applicable).

As part of SDV, subject notes and the CRF should be reviewed for evidence of any adverse events. Any Adverse Events noted in the CRF must be recorded in the source notes and vice versa.

The research team must notify the Sponsor immediately and within 24 hours of becoming aware of a serious adverse event (SAE)/suspected unexpected serious adverse reaction (SUSAR).

The monitor should check that the appropriate form has been completed and signed by the appropriate and delegated individual and submitted to the Sponsor and acknowledgement received and filed in the Site File.

SAEs are defined as:

- Serious and treatment related
- Serious, not treatment related and not listed as an expected event within the protocol

SUSARs are defined as:

- An adverse reaction, the nature or severity of which is not consistent with the applicable product information" (i.e. IB or SPC)

For all CTIMPs, the monitor will ensure that an annual Development Safety Update Report (DSUR) has been completed and submitted in a timely manner.

8. Randomisation/Unblinding Processes

<insert details regarding the blinding/unblinding arrangements for this trial including the system to be used, the Sponsor reporting timeframe, process for unblinding and documentation requirements>

The monitor will ensure that there is adequate documentation of the randomisation and unblinding processes (where applicable) recorded within the Site File.

The monitor will ensure that <delete as appropriate: code break envelopes are available at all times/staff have access to the randomisation system>. If there has been a need to unblind a particular subject, the monitor should ensure that the reason is documented in the participant's notes, in the CRF and in the monitoring visit report.

The Sponsor must be informed of any unblinding within 24 hours of the site becoming aware of the unblinding.

9. Out of Range Laboratory Results

Laboratory results must be reviewed within 7 days by the appropriate and delegated individual. The results must be annotated with a statement of clinical significance or non-clinical significance, this should be signed and dated by the reviewer. Clinically significant results must be followed-up with an appropriate action.

10. Investigational Medicinal Products/Accountability

The frequency of visits to the pharmacy department will be variable during the life of the study, but it would be expected that pharmacy visits will be completed at/prior to initiation and at each monitoring visit thereafter.

Drug accountability will encompass:

- Delivery
- QP Release
- Receipt
- Storage
- Temperature monitoring – Clinical Trials is monitored by Tutela, records will be checked
- Dispensing – Pharmacy accountability logs to be checked, prescriptions
- Returns – bottles to be checked

<insert any trial-specific arrangements or requirements>

11. Trial Master File/Investigator Site File (TMF/ISF)

The relevant Trial or Investigator Site File will be reviewed at the SIV and then as appropriate at interim visits. Any items missing from the file should be documented in the monitoring visit report. The monitor should check that missing items have been filed at the next visit (on-site or remote).

Details of all new study personnel, the Delegation of Authority and Signature Log and evidence of training for any new entries will be reviewed as appropriate.

12. Sample/Specimen Processes and Storage

Laboratory process and storage systems/temperature monitoring/emergency processes will be reviewed as appropriate. The monitor will ensure that shipment requirements and processes have been adhered to and documented evidence is available. The monitor will ensure that records of relevant calibration/maintenance records are available for equipment where appropriate.

13. Data Collection and Management Pl, Data Storage/IT Security, and Statistical Analysis Plan

The monitor will ensure that an effective Data Management Plan is in place (where appropriate/necessary) in addition to confirming that there are appropriate and secure measures in place for all data whether electronic/paper. Electronic records must have restricted access and be password protected.

Where data is being accessed from an external source (e.g. HSCIC), the data sharing agreement should be examined to ensure compliance with the terms and conditions of the agreement.

14. Finance/Contracts

The monitor will ensure that there are processes and evidence in place for all payments for ancillary services and patient expenses.

15. Communication

Email communication between the site and the monitor should be filed in the Site File.

16. On-site Monitoring Visit Reports and Remote Monitoring Visit Reports

On-site Monitoring Visit reports will be produced by the monitor, and sent to the relevant site staff for their review, along with a summary of the findings. This report will be forwarded to the relevant site staff within 21 calendar days of the on-site monitoring visit. Remote Monitoring Visit reports will be produced by the monitor and sent to the site for action.

For on-site and remote monitoring visits, unless otherwise specified, the site must respond to the findings raised within 28 calendar days. The response will be in the format of the Corrective Action and Preventative Action (CAPA) response document. The monitor will review the responses and close out findings that have been satisfactorily resolved. Any unresolved findings/actions will be marked for additional review and additional actions may be requested from the site.

Once all findings have been satisfactorily resolved, the monitor will closed the Monitoring Visit and CAPA Reports and inform the site. A signed copy of the report and responses must be kept in the Sponsor file and also in the Site File for reference.

17. Escalation of Issues

Where there are significant non-compliance issues identified these must be highlighted to an appropriate member of the study team during the visit, documented in the monitoring report and followed up by written communication with the Principal and/or Chief Investigator as appropriate and the actions/resolutions documented. Non-compliance will be escalated as per SOP S-1016 and in the case of a serious breach as per SOP S-1013. The resolution should be followed up at the next visit to site.

Monitoring Plan Author (Print Name):	
Role:	
Version and Date of Monitoring Plan:	

Next Review: Annually, at the same time as DSUR submission or upon next substantial amendment.

Monitoring Plan Amendment History

Amendment No.	Monitoring Plan Version No.	Date Issued	Author(s) of Changes	Details of Changes Made

Record of Monitoring Visits Completed

<Append a record of monitoring visits completed at the end of the trial or upon each review of the Monitoring Plan>