King's Health Partners Clinical Trials Office
Monitoring Plan *(for Clinical Trials Sponsored by King's Health Partners)*

Protocol Title	
Site	
Chief Investigator	
Sponsor	
EudraCT Number	
R&D Number	

Date of Release	
Version Number	

Author:	*Print name*	*Sign*	*Date*
Authorised by:	*Print name*	*Sign*	*Date – should be same date as version number of document.*

DOCUMENT HISTORY

Version	Date	Section	Description
1.1	05Aug08		Initial Release
1.2	23Mar10		Document transferred to KHP header information and document key updated to accommodate the new headers and footers.
1.3	13Jun12		Administrative changes to KHPCTO
1.4	29Aug12		Minor administrative changes

If there is an update to a section of the monitoring plan the entire document should be released with a new version number and the document history page completed.

Document Key	
Regular black text	Suggested content
Green italics	*Instructions*
Blue Italics	*Optional text*
Note on headers & footers	*Front page: The footer at the bottom should detail the KHP-CTO version of the document.* *All other pages: The header is formatted to auto update to the name of the document (you can also right click and select update field to do this) Please ensure that the name of the document reflects the current version and date of the trial specific document.*

This table is for CRA information only and should be removed prior to finalisation.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
CCF	Contact Comment Form
CI	Chief Investigator, responsible for overseeing all clinical trial sites in a multi-centre trial.
CRA(s)	Clinical Research Associate(s) who monitor clinical trials sponsored or co-sponsored by King's Health Partner Organisations to ensure GCP compliance
CRF	Clinical Record Form/ Case Report Form
CRO	Clinical Research Organisation
CTA	Clinical Trial Authorisation
CV	Curriculum Vitae
DCF	Data Clarification Form
DSMB	Data Monitoring Committee
FDA	Food and Drug Administration *(US regulatory agency)*
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare products Regulatory Agency
MVR	Monitoring Visit Report
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
Investigator	Clinician responsible for running a clinical trial. **Sub-**Investigator may be used to describe additional clinicians who assist in the running of a clinical trial.
ISF	Investigator Site File
IVRS	Interactive Voice Response System
King's Health Partners	King's Health Partners Academic Health Science Center is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas'. King's College Hospital and the South London & Maudsley.
PI	Principal Investigator, responsible for a single clinical trial site in a multi-centre trial.
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
REC	Research Ethics Committee
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
REC	Research Ethics Committee
R&D	Research & Development
TMF	Trial Master File
KHP-CTO	King's Health Partners Clinical Trials Office

1. TRIAL SUMMARY

Primary objective of trial	
Trial Timelines	
Planned number of subjects in the trial	
Number of centres *(If multi centre)*	
Number of subjects per site *(If multi centre)*	
Subject numbering system	*How will subject numbers be allocated*
External partners involved	*e.g. CROs, IMP management/provision*
CRF	*Paper / Electronic*
Data entry and query responsibilities	*External management company or internal by site staff*
Randomisation	*IVRS / Coded list*
DMC	*Data review intervals if applicable*
Central laboratory	

(Table may be amended as necessary to include further trial specific details)

2. TRIAL START UP

2.1. KING'S HEALTH PARTNERS CLINICAL TRIALS OFFICE AND TRIAL CONTACTS

Regarding quality and monitoring issues the CRA is the first line of contact for trial site staff and investigators; the second line of contact is the Quality Manager. *In a multicentre trial, the first point of contact for trial sites regarding any other issues is the Trial Management Team.*

Contact Details

Job Title	Name	Contact Details
CRA		
Quality Manager		
Pharmacovigilance		
R&D		
External Partners		
Central Labs		

Add additional rows as appropriate.

3. REFERENCE DOCUMENTATION TO BE USED FOR THIS TRIAL

Where there are no SOPs in place for managing a trial the KHP-CTO SOPs and guidelines will be followed.

SOP Title	Author Department/Company
e.g. Clinical Trial Monitoring	*KHP-CTO*

Please see appendix…..for current version information.

3.1. PRE-TRIAL COMMENCEMENT

The CRA will assist sites in start-up activities and will, in conjunction with the Quality Manager, ensure that the MHRA CTA Application is completed to a satisfactory standard. Investigators remain responsible for Ethics and R&D Applications, however CRAs may assist if deemed necessary and appropriate. All contact prior to trial commencement should be documented and filed in the appropriate trial site, TMF or R&D files.

In most multi-centre trials the CI will select the other participating sites; if this is the case the following may be used.

The CI will approach and select all other sites to participate in the trial. The coordinating centre will facilitate application for the relevant local approvals by the individual sites; the nominated CRA/ CQM may provide guidance as necessary. All pre-trial contacts will be documented and filed. The R&D department will facilitate the set up and approval of all site agreements and co-sponsorship agreement (if appropriate).

3.2. ESSENTIAL PRE-TRIAL DOCUMENTS

Depending on trial classification different documentation may be required. As a rule the checklist from R&D, Ethics and MHRA CTA application forms should be used to determine what is required however it is good practice to maintain a central list as below.

The trial will not be allowed to commence at site until all necessary approvals have been granted and all essential documentation listed below is present in the ISF and has been verified by the CRA.

Document	*Original required?*	*Frequency of update required*
e.g. PI CV	*Yes signed and dated*	*12 Months*
Completed Delegation log	*Yes*	*As necessary*

The CRA will also work with the site staff to ensure that all required trial materials are present at site in sufficient quantities prior to initiation. Details of these are found below.

Material	*Quantity Required*	*Re-supply procedure*
CRF	*10*	*Print off secure computer*
Lab Kits	*40*	*Order through pharmacy*

3.3. INITIATION OF THE TRIAL

All sites will have an initiation visit prior to the trial starting. Initiation Visits will be conducted at each investigator site except where no IMP is to be administered. Site initiation may be performed for these sites during the Investigator meeting if all aspects of the initiation visit checklist can be completed with the exception of the Pharmacy Visit section.

As per Initiation SOP – Investigator sites must be visited by the CRA unless there is no IMP intervention and Pharmacy involvement at the site and all aspects of the initiation visit were conducted during the Investigator Meeting.

The following points will be discussed at the initiation meeting *(this is the minimum requirement and can be added to as necessary)*:

- Primary and secondary endpoints
- Definitions of source data
- Safety reporting requirements and responsibilities
- Data protection / patient privacy
- CRF completion procedures / Data management
- Randomisation procedures
- Patient compliance
- Handling of samples and scans
- Trial reference manuals *(If applicable)*
- Pharmacy and dispensing of IMPs
- Maintenance of the ISF

3.4. TRIAL CRA

The CRA must be familiar with the protocol and relevant SOPs prior to the start of the trial. If further training is required this will be undertaken with the assistance of the KHP-CTO Training Executives.

If there is a change of a trial CRA, a full handover will be completed. Where the CRA is unexpectedly absent, monitoring cover will be provided by the KHP-CTO.

4. INVESTIGATIONAL MEDICINAL PRODUCTS

The CRA will ensure that IMP shipment and receipt documentation are complete, accurate and in accordance with handling requirements of the SmPC or Investigator's Brochure.

4.1. QP RELEASE OF IMP

The CRA will check that all QP release documentation is in place prior to trial start.

Include details here of how IMP is to be QP released and state what duties the CRA must complete to ensure this is done accurately.

If IMP is manufactured for CT use and provided free by a Pharmaceutical company it is often provided in bulk. It may not be labelled for clinical trial use or packaged appropriately for the trial. Under these circumstances re-packaging and QP release is required. GSTFT is the preferred provider for all Partner Organisations, however an external preferred provider may be used if GSTFT are unable to meet the necessary requirements.
The CRA will liaise with the Clinical Trials Pharmacist to coordinate these activities. Please state who the named QP will be and what documentation is necessary.

If site is purchasing licensed IMP and using it as per label specifications it may not need QP release. If IMP is repackaged or relabelled (the local pharmacy label is allowed without QP) in any way then QP release will be required. In addition, QP release will be required if the co-ordinating centre is distributing IMP to other participating sites in a multi-centre trial.

4.2. TRACKING OF EXPIRY DATES

The CRA will check the expiry dates of the IMP on a regular basis and work with Pharmacy to ensure that there is sufficient quantity of valid IMP onsite for the continuation of the trial.

4.3. ACCOUNTABILITY, STORAGE AND HANDLING OF IMP

The CRA is responsible for checking the IMP accountability and IMP reconciliation of the IMP both at individual (amount dispensed/used/returned by subject) and site level (total delivered, used, unused, and returned/destroyed by trial site). The CRA will also check that the IMP is being stored and handled according to the requirements of the protocol information *(IB, SmPC, Label)*.

4.4. RETURN AND DESTRUCTION OF IMP

The CRA will verify accountability and reconciliation prior to destruction or return as follows: *Describe what will be done with used / unused IMP at the site and what must be verified. If IMP is to be returned to an external partner, please replace blue text below with full instructions for IMP return.*

Pharmacy will destroy returns or expired items as per local Pharmacy SOP and full documentation will be kept in the pharmacy file. Destruction of IMP should not occur until accountability has been completed and approval for destruction given by the Chief Investigator and the Sponsor Representative i.e. KHP-CTO. Interim accountability and destruction may be permitted.

5. MONITORING AND SUPPORT ACTIVITIES DURING THE TRIAL

5.1. TIMING AND FREQUENCY OF MONITORING VISITS

The following SOP will be followed:

- *KHP-CTO Clinical Trial Monitoring*

In most cases this will be the KHP-CTO Monitoring SOP however if this is not the case please give details of external guidelines to be used.
The frequency of monitoring visits is determined by a risk assessment of the trial.

The first monitoring visit following initiation of the site and trial commencement will take place within approximately ……. *weeks* after the inclusion of the first patient. Subsequent monitoring visits will take place every ……. *weeks.*

The interval for monitoring visits may be longer or shorter than stated above, dependant on subject enrolment rate, quality issues, trial site compliance or other trial site issues.

Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring visit report and the monitoring plan amended if appropriate.

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

5.2. ACTIVITIES DURING THE MONITORING VISITS

The following SOPs will be followed:

- *KHP-CTO Clinical Trial Monitoring*
- *Notification of Serious Breach of GCP*

The trial CRA will sign the trial monitoring visit log at every visit. The dates on the log should correspond to those on the monitoring visit reports and follow-up correspondence with the site.

In addition to activities specified in the SOPs above the CRA will focus on the following items *(these are trial specific and should be amended as necessary)*:

- *Review data issues*
- *Informed Consent of patients (100% must be verified)*
- *Inclusion / Exclusion criteria*
- *Safety reporting*
- *Verify CRF and DCF status*
- *Discuss any deviations or protocol violations with investigator and take action as appropriate (e.g. amendments, inform CI, MHRA or Ethics)*

Any key issues (any issue that would impact on the integrity of data and subject evaluation) identified during the monitoring visit (including non-compliance, discrepancies, suspicion of misconduct or fraud) must be immediately reported to appropriate personnel, documented and followed up to resolution.

5.2.1. SOURCE DATA VERIFICATION PLAN

Source data verification will be performed by the trial CRA for *(100%)* data in the CRF for *(100%)* of subjects. If it is observed that an unacceptable level of discrepancies arise the CRA will retrain site staff. If after such retraining data accuracy is still not considered sufficient the CRA will escalate the issue to their line manager and Quality Manager who will review the risk assessment for the trial and the level of monitoring required.

If 100% SDV will not be performed on 100% data for all subjects please specify the trial data to be monitored; the percentage of subjects and percentage of data per subject to be verified and how the plan may be modified based on findings of SDV.

Percentage of required source data verification will be detailed on the trial risk assessment form.

5.2.2. SOURCE DOCUMENTATION

Define what documents will be considered as source documents on a source data location list. Identify any sections of the CRF that will be considered as source data (e.g. patient diaries, questionnaires and trial assessments). If appropriate, source data checklists may be used to assist verification. If any source data is in electronic format and will not be printed off to be verified; the CRA must ensure that this is evidenced on the source data location list and that full details of what must be checked and when should be listed above.

The following documents will be considered as source data:

- *Patient record (including printed scan reports and blood sampling initialled by a trial doctor)*
- *Patient diaries*
- *Quality of life questionnaires*

Information on where to find specific data points for the trial will be detailed on the source data location list stored in the site file. *(Template copy in appendix……)*

5.2.3. STATUS OF TRIAL SUBJECTS

At each monitoring visit and at regular intervals between visits the CRA will contact the sites to discuss the status of trial subjects (screened, treated, ongoing, and discontinued) enrolled into the trial.

5.2.4. PRIMARY END POINT DATA

During monitoring visits the following endpoint data should be verified:

State details of what data the CRA should review to verify the primary and secondary endpoint data e.g. ensure that relevant tests/assessments are done at the correct time. Include details on any SDV checklists that can be used by the CRA to ensure that all required data is verified.

5.2.5. COMPLIANCE TO TREATMENT REGIMEN AND IMP ACCOUNTABILITY

The following SOPs will be followed:

- *KHP-CTO Clinical Trial Monitoring*
- *(list others as appropriate)*

Specify actions CRA should complete during monitoring visits.

The CRA will verify adherence to the clinical trial protocol and that trial subjects receive correct medication in the correct doses at the correct times. Any discrepancies (missed doses, incorrect timings) will be documented. *Insert details of any data critical to evaluation if the IMP (e.g. peak/trough pharmokinetic evaluations, dose in relation to meals).*

Documentation for assigned treatment must be consistent across source data, dispensing logs and CRF records. *Other documentation may also need to be verified against hospital logs e.g. electronic dispensing print-outs, IVRS confirmation faxes.*

5.2.6. SAFETY REPORTING

The following SOP will be followed:

- Pharmacovigilance and Safety Reporting Policy
- *List any other relevant documentation.*

In addition to the above SOPs and the trial protocol the CRA will verify the following:

- All SAEs/follow up reports have been reported to the Sponsor/Chief Investigator/Ethics committee as required by UK regulations.
- All required SAE data are recorded in the CRF and consistent with source data and SAE forms.
- All documentation is filed in the TMF/ ISF.
- All periodic safety updates and summaries are sent to MHRA and Ethics Committee as required.

5.2.7. BIOLOGICAL SAMPLES (BLOOD, URINE, PK SAMPLING)

The CRA will verify that the protocol requirements have been met regarding timing, storage, shipping and documentation of biological samples.

5.2.8. TRIAL MASTER FILE (TMF) AND THE INVESTIGATOR SITE FILE (ISF)

The following SOP will be followed:

- *KHP-CTO Clinical Trial Monitoring*
- *Creation and Maintenance of Trial Master Files and Essential Documents*

Choose the most appropriate wording:

Single Centre Trials

The TMF will be checked for completeness by the CRA at regular intervals throughout the trial.

Multi-centre Trials
The TMF will be maintained by the Chief Investigator and checked for completeness by the CRA at regular intervals during monitoring. The CI will maintain a site specific TMF file for each participating site containing all essential documentation and pertinent correspondence for that site.

Each site will maintain an Investigator Site File for the trial which will also be checked for completeness by the CRA. All administrative documentation and correspondence for the trial should be filed here.

The site specific TMF section will be reconciled with the Site specific Investigator Site File at regular intervals to ensure that the TMF documentation remains current however no patient identifiable data will be filed in the TMF.

5.2.9. FURTHER TRIAL SUPPORT

The following SOP will be followed:

- *Maintaining a Clinical Trial Authorisation*

The CRA may assist the site in compiling and submitting amendments to Ethics Committee and R&D department however this remains a site responsibility. Amendments required for the MHRA will be facilitated and processed by the CRA and Quality Manager or delegate.

5.3. MONITORING VISIT REPORT AND FOLLOW-UP LETTER

The following SOPs will be followed:

- *KHP-CTO Clinical Trial Monitoring*
- *(list others as appropriate)*

The CRA will fully document each monitoring visit in a Monitoring Visit Report which will be reviewed by the Quality Manager or delegate. Follow-up correspondence will be sent to site in a timely manner after the visit. All follow-up actions will be followed until resolution. All discrepancies that cannot be resolved will be documented in a file note and signed by the CRA, relevant site staff and PI/CI.

5.4. OTHER CONTACT AND CORRESPONDENCE

The following SOPs will be followed:

- KHP-CTO Clinical Trial Monitoring
- *(list others as appropriate)*

All pertinent correspondence with site staff will be documented appropriately (e.g. follow-up letter, contact comment forms, e-mails) and filed in the *TMF/ISF* as applicable.

5.5. CRF AND QUERY MANAGEMENT

The following SOPs will be followed:

- *KHP-CTO CRF Design*
- *(list others as appropriate)*

The CRA will perform SDV as described in 5.2.1. In addition, quality checks will be performed to ensure that the CRFs have been completed in accordance with relevant guidelines – in particular the CRA should ensure that the header information is complete and that appropriate edit practices have been followed. All CRFs monitored during a visit will be detailed in the Monitoring Visit Report.

Optional text to be used if the CRFs must be sent to another site or external data management company.

The CRA will verify that all completed CRF forms have been sent to ……(insert relevant details) by …… (e.g. fax).

If the trial is sponsored by partner organisations the following may also be required.

A data base check for accuracy of data entry will be performed at…….(insert time points agreed with Quality Manager). The data points to be checked are as follows:

- *End point data*
- *Safety data*
- *Insert others as applicable*

6. TRIAL CLOSE OUT

Specify what and how trial materials will be returned, destroyed or retained by the trial site.

At the end of the trial once all data and documentation has been completed the CRA will perform the Close-out Visit *(this may be reported on an MVR if no documentation has been developed).* The visit will include final review of all trial documentation including Pharmacy files for completeness. After the final visit the CRA will record all information in a written report. Ideally all outstanding actions will be completed prior to the Close-out Visit however the CRA should follow up all ongoing actions until completion ensuring that all correspondence and documentation is filed.

7. ARCHIVING

The following SOPs will be followed:

- *Archiving of Clinical Trial Data and Essential Information*

Once all trial actions have been completed and the trial data has been locked the CRA will work with the Site staff and the Archive Specialist to archive the trial documentation.