Hull and East Yorkshire Hospitals NHS
NHS Trust

R&D Department

Site initiation of multi-centre HEY-sponsored CTIMPs

When this document is viewed as a paper copy, the reader is responsible for checking that it is the most recent version.

The current version is available on the HEY internet Research & Development site
Click on GCP SOPs for HEY-sponsored CTIMPs
http://www.hey.nhs.uk/rd

Or the HEY intranet Research & Development site
Click on GCP SOPs
http://intranet/rd/

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Author:	**J H Pacynko and J Illingworth**
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Distribution:	**R&D internet and intranet site**
Signed off by R&D Director:	**Professor Nick Stafford**
Signature:	***Signed and dated copy kept in R&D***
Date:	
Signed off by R&D Manager:	**James Illingworth**
Signature:	***Signed and dated copy kept in R&D***
Date:	

This page should detail the version history for this SOP and the main changes corresponding to the versions.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 27.10.10	J Pacynko	Original SOP approved by R&D Committee on 27.10.10.
Version 2, 08.03.11	J Pacynko	Change of title of PI responsibilities to PI Agreement. PI Agreement is now a separate document, not part of the contract. Safety reports added to ISF contents checklist. Wording of PI agreement up-dated. Addition of Site Assessment Checklist.
Version 3, 24.03.11	J Pacynko	Improvement to CRF section of PI Agreement.
Version 4, 14.11.13	J Pacynko	Review PI Agreement changed to PI Responsibilities Site initiation report added as part of Sponsor checks PI Responsibilities amended
Version 5, 20.04.15	J Pacynko	Changes of wording – in red type Addition of pharmacy section

Please note

- **For definitions of acronyms refer to Appendix 2 of Management of SOPs.**
- **Refer to Appendix 3 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.**
- **Contact either the R&D QA Manager or Monitor for access to documents referred to in this SOP which are only available on the Trust's Y: drive in GCP SOPs & forms.**

1 Introduction, purpose and who should use this SOP

- All CTIMPs must be conducted according to the UK Clinical Trial Regulations and may be inspected by the UK competent authority, the Medicines and Healthcare products Regulatory Agency, in order to check compliance with the Regulations.

- Multi-centre CTIMPs are clinical trials of investigational medicinal products that have more than one centre/research site.

- The benefits of multicentre trials include (1) being able to recruit a larger number of participants from different geographic locations, (2) the possibility of inclusion of a wider range of population groups and (3) the ability to compare results among centres.

- The lead research site has a Chief Investigator (CI) and the other research sites have a Principal Investigator (PI) for each site. The CI takes primary responsibility for the conduct of the multi-centre study whereas PIs have responsibility for the conduct of the study at their site.

- The purpose of this SOP is to describe what approvals and documents are required at each participating research site prior to the initiation of the site in order to comply with the UK Clinical Trial Regulations.

- This SOP should be used by all investigators involved with HEY-sponsored multi-centre CTIMPs. It is particularly relevant to the Chief Investigator, trial co-ordinator and all other research staff at the HEY lead research site.

- If the study is set up and managed by a Clinical Trials Unit rather than the HEY lead site, then this SOP should be used by the relevant CTU staff.

- This SOP should also be used by all HEY R&D staff and all HEY pharmacy staff involved with clinical trials.

2 Principal Investigator responsibilities

- To ensure the following approvals and documents are in place in the **Investigator Site File** (ISF) prior to site initiation:

  Approvals
  - A copy of the MHRA notice of acceptance (for the study and amendments)
  - A copy of the REC favourable opinion (for the study and amendments)

- A copy of the HEY R&D approval (NHS permission) as lead site (for the study and amendments)
- The original signed and dated participating site SSI form
- The original participating site R&D approval

Site feasilbility or expression of interest form

- A form completed by the site confirming their willingness to take part in the study, the expected number of patients to be recruited at the site and that it is feasible for the site to carry out the study (signed by PI).
- This enables sites to assess and resolve potential issues which may hold-up the start of the study at site or prevent recruitment.

Site initiation report

- To document that the trial documents and procedures were reviewed with the research and pharmacy staff prior to the start of the study (signed by PI and trained staff).

Clinical Trial Site Agreement (CTSA)

- An original fully signed and dated CTSA including:
  - Payments made to sites
  - Suitable indemnity/insurance arrangements for the site
  - Archiving arrangements of Investigator Site File and CRFs with details of address of archive, contact details of archivist, list of trial files and allowed date of destruction

Principal Investigator Delegation of Duties

- Appendix 2 is a template of the duties/functions delegated to the PI by the CI and Sponsor. This may be modified according to the trial arrangements and may be incorporated into the site contract rather than kept as a separate document.

Study documents

- The current approved version of the protocol
- The current approved version of the patient information sheet
- The current approved version of the informed consent form
- The current approved version of the GP/hospital consultant letter (as applicable)
- Any other REC approved study documents
- Patient study cards
- The current version of the CRF including:
  - Inclusion/exclusion criteria checklist to be signed off by PI or delegated doctor
  - Instructions for randomisation
  - Instructions for safety reporting
- Instructions for the informed consent procedure
- Instructions for lab procedures (if applicable)
- Instructions for unblinding (if applicable)
- Instructions for pharmacy (if applicable)
- SAE initial and follow-up report forms (or link)
- Summary of Product Characteristics (link to website – electronic version to be used as expectedness reference)

Site Research Staff

- The original delegation and signature log (fully completed and signed)
- The contact sheet with up-to-date contact details for each staff member
- Original signed and dated CVs of all site staff involved with the study.

- Copies of GCP training certificates of all site staff involved with the study.

ISF checklist

- **The original ISF checklist signed off by the Principal Investigator.**
- **The ISF checklist includes the above approvals and documents**
- **A suggested checklist is in Appendix 1.**

3 Participating site pharmacy responsibilities

- To ensure the following documents are in place in the **Pharmacy Study File** (PSF) prior to site initiation:

Pharmacy green light

Pharmacy section of site initiation report

- To document that the trial documents and procedures were reviewed with pharmacy staff prior to the start of the study.

Study documents

- The current approved version of the protocol
- Instructions for pharmacy (pharmacy manual)
- Instructions for randomisation (if applicable)
- Instructions for unblinding (if applicable)
- Summary/ies of Product Characteristics (link to website – electronic version to be used as expectedness reference)

CT Pharmacy Staff

- The delegation and signature log (completed by all site staff including pharmacy staff involved with the study)
- Pharmacy signature sheet (if applicable)
- The contact sheet with up-to-date contact details for study staff
- Signed and dated CVs of pharmacy staff on the delegation log.
- GCP training certificates of pharmacy staff on the delegation log.

Relevant regulatory information

PSF checklist

- The PSF checklist signed off by CT pharmacy. A suggested checklist is in Appendix 3.

4 Chief Investigator responsibilities

- To ensure the following approvals and documents are in place in the **Trial Master File** prior to site initiation:

For the study:

- The original MHRA notice of acceptance (for the study and amendments)
- The original REC favourable opinion (for the study and amendments)
- The original HEY R&D approval as lead site (for the study and amendments)
- The current approved version of the protocol and superceded versions.

- The current approved version of the patient information sheet and superceded versions
- The current approved version of the informed consent form and superceded versions
- Any other REC approved study documents (and superceded versions)
- An example of the patient study card
- The current approved version of the GP/hospital consultant letter (as applicable) and superceded versions
- The current version of the CRF and superceded versions

From the participating site to be initiated:

- A copy of the SSI form (signed and dated by the Principal Investigator)
- A copy of the site R&D approval
- An original fully signed and dated site contract (model clinical trial agreement)
- An original fully signed and dated Principal Investigator Responsibilities
- A copy of the site delegation and signature log (fully completed and signed)
- A copy of the site staff contact sheet (up-to-date)
- Copies of CVs (signed and dated) of all site staff involved with the study
- Copies of GCP training certificates of all site staff involved with the study.
- **A copy of the ISF checklist signed off by the Principal Investigator. Appendix 1 is a suggested ISF checklist.**

5 Sponsor responsibilities

- Once the Sponsor (HEY R&D manager) receives a copy (electronic or paper) of the following documents from the Chief Investigator or trial co-ordinator then the Sponsor will email the 'green light' letter to the PI instructing the site to start the study.

  - Clinical Trial Site Agreement (fully signed)
  - Principal Investigator Delegation of Duties (fully signed, may be part of CTSA)
  - Site initiation report (signed by trial co-ordinator/trained staff)
  - ISF checklist signed off by the PI
  - PSF checklist signed off by pharmacy
  - Local site R&D approval
  - Local site pharmacy greenlight

- Appendix 3 is the template for the sponsor 'green light' letter allowing a research site to start. The original signed copy will be sent to the PI for filing in the ISF.

- All the above documents will be saved electronically in the Y: drive in GCP SOPs & forms in the Green Lights section of the study folder. Paper copies will be kept in the Sponsor Study File in the R&D office.

6 Implementation

- Implementation of this SOP will conform to the process outlined in **R&D SOP 01 Management of SOPs**

Appendix 1

Study title:	**Eudract no:**
Principal Investigator:	**Hospital/GP address:**
Chief Investigator:	**Sponsor: Hull and East Yorkshire Hospitals NHS Trust**

INVESTIGATOR SITE FILE

CONTENTS CHECKLIST

Documents in bold type must be present in the file before site initiation. Principal Investigator to sign off and send this form to HEY lead site/CTU when all documents in bold are present.

This file will hold original essential study documents, please keep in a secure location. At study end, this file will require secure archiving but will need to be readily available upon request.

Section No.	Section	Contents	Document version	Tick if documents present
1	Research staff	**Site Staff Contact Sheet**	Copy	☐
		Delegation & Signature Log	Original	☐
		CVs (signed and dated) of staff on Delegation Log	Originals	☐
		GCP training certificates of staff on Delegation Log	Copies	☐
2	Patients	Study Patient Screening & Recruitment Record	Original	☐
		Study Patient Identification List	Original	☐
		Example Informed Consent Form	Copy	☐
		Example Patient Information Sheet	Copy	☐
		Patient study cards	Copy	☐
		Example GP/hospital consultant letter	Copy	☐
		Signed Informed Consent Forms	Originals	☐
3	Study documents	**Protocol**	Copies	☐
		Protocol amendments	Copies	☐
4	CRFs	**Patient data collection forms**	Originals	☐
		Data queries	Copies	☐

5	Serious adverse events	SAE initial and follow-up report forms	Originals	☐
6	Laboratory tests	**Instructions for lab procedures** (if not in CRF)	Copy	☐
		Normal Ranges & updates (if applicable)	Copy	☐
7	Agreements & site initiation	**Site feasibility/EoI form**	Original	☐
		Site initiation report	Original	☐
		Clinical Trial Site Agreement (fully signed)	Original	☐
		PI Delegation of Duties (fully signed)	Original	☐
8	Approvals	**MHRA notice of acceptance**	Copy	☐
		REC favourable opinion	Copy	☐
		Site-Specific Information Form (signed & dated by PI)	Original	☐
		Local site R&D approval letter	Original	☐
		Local site R&D approval letters for protocol amendments (if any)	Originals	☐
9	Information	Notification of any safety information	Copy	☐
		Notification of information on study amendments	Copy	☐
		Newsletters from Chief Investigator	Copy	☐
		Summary of Product Characteristics (SPC) File Note with weblink to SPC	Copy	☐
		UK Clinical Trial Regulations File Note	Copy	☐
10	Correspondence	Emails, letters, file notes etc.	Copies	☐

As Principal Investigator,
I confirm that the documents in bold type are present in this Investigator Site File.

Name: _____ **Signature:** _____ **Date:** _____

(Insert sending instructions) Please sign and date when all documents in bold are present and email (insert email address) or fax (insert no.) on the same day, marked for the attention of (insert name).

Appendix 2

Study title:	**Eudract no:**
Principal Investigator:	**Hospital/GP address:**
Chief Investigator:	**Sponsor: Hull and East Yorkshire Hospitals NHS Trust**

Principal Investigator Delegation of Duties

The Chief Investigator (insert name) and Sponsor (Hull and East Yorkshire Hospitals NHS Trust (HEY) R&D department) delegate the following duties to the Principal Investigator to ensure that the (insert acronym) trial is conducted according to the UK Clinical Trial Regulations and GCP.

Duties delegated to Principal Investigator

Site-specific Information Form

- To complete and submit the SSI form to the local site R&D department. HEY lead research site/CTU will provide guidance and a template SSI form.

Delegation

- To ensure the completion of the study *Delegation and Signature Log* prior to the start of the study to confirm all the research staff involved with the study and their delegated duties. The signature and initials of staff ensure they can then be identified on forms, medical records etc.
- To keep the *Delegation Log* up-to-date on an ongoing basis.
- To send the up-to-date *Delegation Log* to HEY lead site/CTU annually or upon request to allow central monitoring of the log.

Training

- To ensure all research site staff who are involved with the study are familiar with the protocol and have been trained in the study procedures (including informed consent procedure and safety reporting).
- To ensure GCP training of all site staff is up-to-date.

Investigator Site File

- To keep all study documents and correspondence in an *Investigator Site File (ISF)*. This file will be provided by the lead site/CTU.
- To sign off the ISF contents checklist and send to the lead research site to confirm the necessary study documents are in place prior to the start of the study.

Study medication

- To ensure all procedures regarding study medication are followed according to the protocol and pharmacy instructions.

Study equipment

- To ensure any equipment used during the course of the trial is maintained, serviced and calibrated according to local Trust policy.

Study start

- To ensure that the following are in place prior to the *first patient being consented* and entered into the study and prior to any screening procedure being done:
    - **Local pharmacy greenlight**
    - Local site R&D approval (NHS permission)
    - Site Agreement (fully signed)
    - Investigator Site File
    - **HEY R&D sponsor letter – the green light for the study to start.**

Protocol

- To conduct the trial in compliance with the protocol approved by the MHRA, Research Ethics Committee (REC) and Trust (HEY and local).

- Not to deviate from or change the protocol without agreement from the Chief Investigator, CTU and HEY R&D.
- To notify lead HEY site/CTU promptly of any protocol deviations.
- To notify Chief Investigator/lead HEY site/CTU/HEY R&D of any serious breaches **within 24hrs** of knowledge of serious breach.

Consent

- To check that the *latest REC and R&D (local and HEY) approved versions* of the informed consent form (ICF), patient information sheet (PIS) and GP/hospital consultant letter are used when recruiting patients.
- To ensure that only the PI or Co-investigators (study doctors) on the study *Delegation Log* answer the final patients questions and countersign the consent form after the patient. (Insert research nurse if delegation approved by REC).
- To ensure that the ICF is signed and dated by the patient and study doctor (and insert research nurse if applicable) before any study related procedure is performed (including screening).
- To keep the fully signed and dated original ICF in the Investigator Site File.
- To give one copy of the signed ICF to the patient.
- To file one copy of the signed ICF in the patients casenotes/medical records together with a copy of the PIS, the letter sent to the patient's GP/hospital consultant and the signed inclusion/exclusion criteria checklist.

GP/hospital consultant letter

- To send out the GP/hospital consultant letter ideally on the day of consent or shortly after the date of consent.

Case report forms (CRFs) and data queries

- To ensure the accuracy and legibility of CRFs (patient data collection forms).
- To complete CRFs as fully as possible.
- To send CRFs to the HEY lead site/CTU promptly after each patient visit.
- To resolve and respond to any data queries generated by the lead HEY site/CTU **within one month** of receipt of queries. Insert < Payments will depend on return of outstanding data queries> if applicable.

Patients casenotes

- To ensure patient study visits are clearly recorded in patient's casenotes/medical records as visits occur.
- HEY lead site/CTU will provide guidance. The minimum details to record are*;*
  - *Clearly written date of visit or contact, brief study title/acronym and visit number,*
  - *Date patient given patient information sheet,*
  - *Date consent form signed,*
  - *Date of screening,*
  - *Medical history, concomitant diseases and medication including study medication, and any changes in concomitant diseases and medication at subsequent visits,*
  - *Anything which is relevant to the ongoing care of the subject;*
    - *Relevant results and study medic's assessment of these results.*
    - *Brief description of any AEs with start & stop times/dates and any significant test results or a medical summary of events if more appropriate.*
  - *Any other relevant information.*

Samples

- To ensure that samples are taken, processed, stored and transferred to the central lab for analysis according to the Protocol and Trial Samples Guide produced by HEY lead site/CTU.

Amendments

- To implement any amendments to the protocol which have been notified to you by the Chief Investigator/lead HEY site/CTU after obtaining local R&D approval.

Safety reporting

- To ensure reporting and documenting of all adverse events (serious and non-serious) according to the protocol and as requested in the CRF or by the lead HEY site/CTU.
- Report **all** serious adverse events (SAEs) to the lead HEY site/CTU **within 24 hours** of becoming aware of the event according to instructions provided by lead HEY site/CTU.

- Report additional follow-up information to lead HEY site/CTU as available or upon request until the SAE has resolved or a decision has been taken for no further follow-up.
- To ensure that a study medic assesses the seriousness, intensity, relatedness and unexpectedness of SAEs.
- As PI to review and sign off all SAEs at site. The PI's decision on relatedness and unexpectedness will not be overruled by the CI or Sponsor.
- To file the original signed SAE report forms in the Investigator Site File.
- <Delete this section if not relevant> If a study patient falls pregnant during the course of the clinical trial, follow the instructions in the safety section in the protocol.

End of trial

- To notify the Chief Investigator/CTU and Sponsor immediately of any reason to stop the trial.
- To end recruitment for the trial when notified by the Chief Investigator/CTU.

Archiving

- To archive the Investigator Site File and CRFs in a secure location as stipulated in the site agreement until the allowed date of destruction.
- To obtain permission from the Chief Investigator before destruction of the Investigator Site File and CRFs.

As Principal Investigator, I confirm that I have read, acknowledge and understand the above duties. I acknowledge and understand that:

- **I take responsibility for the initiation and conduct of the study at my site. If I delegate some of the above duties, I still remain responsible for them.**
- **The Sponsor reserves the right to temporarily suspend or terminate the study at my site at any time for reasons including (but not limited to) safety or ethical issues, or severe GCP non-compliance.**
- **An on-site visit by the CI/Sponsor/CTU may be required for serious issues or non-compliance.**

	Name	Signature	Date
Principal Investigator			
Chief Investigator			
HEY R&D Manager			

Appendix 3

Study title:	
R&D ref no:	**Eudract no:**
Principal investigator:	**Hospital/GP address:**
Sponsor: Hull and East Yorkshire Hospitals NHS Trust	

PHARMACY STUDY FILE

CONTENTS CHECKLIST

Documents in bold type must be present in file before site initiation. Pharmacy to sign off and send this form to HEY lead site/CTU when all documents in bold are present.

This file will contain original essential study documents, please keep in a secure location. At study end, this file will require secure archiving but will need to be readily available upon request.

Section No.	Section	Contents	Document version	Tick if documents present
1	Contacts	**Study Staff Contact Sheet**	Copy	☐
		Delegation and Signature Log	Copy	☐
		Pharmacy Signature list	Original	☐
		CVs (signed and dated) of CT pharmacy staff on Delegation Log	Originals	☐
		GCP training certificates of CT pharmacy staff on Delegation Log	Originals	☐
2	Dispensing	**Dispensing procedure**	Copy	☐
		Prescriptions	Originals	☐
		Study Medication Accountability Forms	Originals	☐
3	Study medication	**Emergency code breaking procedure for blinded trials**	Copy	☐
		Emergency code break forms	Copies	☐
		Randomisation instructions/ Randomisation Code Envelopes/List (as applicable)	Originals	☐
		Supply/Receipt/Return Forms	Copies / Originals	☐

Section No.	Section	Contents	Document version	Tick if documents present
3	Study medication contd.	**Sample Labels**	Copy	☐
		Summary of Product Characteristics (file note)	Copy	☐
		Certificate(s) of Analysis of Medication & New Batches	Copies / originals	☐
		Documentation of destruction of medication at study end	Original / copies	☐
4	Study Documents	**Pharmacy manual/instructions**	Copy	☐
		Pharmacy greenlight	Copy	☐
		Pharmacy financial arrangements	Original/copy	☐
		Study protocol and relevant amendments	Copies	☐ ☐
		Study document tracking log	Copy	
5	Regulatory information	Relevant pharmacy MHRA, REC and R&D information	Copies	☐
6	Communication	Emails, study updates, letters, file notes etc.	Copy	☐

As Pharmacy CT representative,
I confirm that the documents in bold type are present in this Pharmacy Study File.

Name: _____ **Signature:** _____ **Date:** _____

(Insert sending instructions) Please sign and date when all documents in bold are present and email (insert email address) or fax (insert no.) on the same day, marked for the attention of (insert name).

Appendix 3

Hull and East Yorkshire Hospitals NHS
NHS Trust

Address of HEY R&D Department
R&D Office telephone numbers

Date of letter

Study title:	
Sponsor R&D ref no: **CSP no.**	**EudraCT no:** **REC ref no**:
Principal investigator:	**Hospital/GP address:**
Sponsor: Hull and East Yorkshire Hospitals NHS Trust	**Participating site:**

Dear Principal Investigator

Regarding the above clinical trial for which you are a participating site, the R&D Office at Hull and East Yorkshire Hospitals NHS Trust has received the following documents:

- Local NHS permission letter dated…
- Site initiation report signed…
- ISF checklist signed…
- A fully signed model clinical trial site agreement dated…
- Principal Investigator Delegation of Duties signed …
- Pharmacy greenlight dated …
- PSF checklist signed…

We are satisfied that the trial co-ordinator/CTU have made the necessary checks to ensure the essential study documents are in place at your site and that research staff have been appropriately trained.

Please take this letter as confirmation from the Sponsor for you to commence recruitment to this study at your site.

Thank you for your participation in this trial.

Yours sincerely

R&D Manager
Hull and East Yorkshire Hospitals NHS Trust