Hull and East Yorkshire Hospitals NHS Trust

Department	Research & Development
Title of SOP	Management of SOPs
SOP reference no:	R&D SOP 01
Authors:	J H Pacynko and J Illingworth
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Next review date:	31.01.21
Target audience:	Research, pharmacy and R&D staff
Distribution:	HEY R&D internet Click on GCP SOPs for HEY-sponsored CTIMPs https://www.hey.nhs.uk/research/researchers/gcp-sops-for-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.

Authorized by		Sign	Date
R&D Director	Professor Anthony Maraveyas		
R&D Manager	James Illingworth		

This page details the version history and the main changes made for each new version.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 27.10.10	J Pacynko	First SOP approved by R&D Committee on 27.10.10
Version 2, 12.07.12	J Pacynko	SOP amended to simplify the process of review, approval and implementation of SOPs. Also that SOP is available on the HEY R&D website.
Version 3, 20.02.14	J Pacynko	At the end of March and September an email will be sent to research staff reminding them of updates to SOPs in the previous 6 months and asking them to sign an SOP Updates Training Record Links and appendices up-dated
Version 4, 13.11.14	J Pacynko	Page 5 Review and up-dating - SOPs will be assigned a review date 3 years after the approval or previous review date. The review date has been changed from 18mths to 3yrs to be in-line with Trust policy CP001 Development and management of procedural documents policy.
Version 5, 31.01.18	J Pacynko S Moffat	**Changes are shown by wording in red.** • In abbreviations section: SSA deleted, SSF deleted, HRA IB and RSI added. • Sending of global email removed and replaced with 6-monthly signing of Training Record to inform research staff of up-dates to SOPs. • Improved definitions of TMF and REC. • SOP updates will now be sent out to research staff approximately every 6 months, previously updates were being sent in March and September but some flexibility is required in case no SOPs had been up-dated within 6 months. • Removal of Appendix 1 and 4 • Checking and updating of hyperlinks in the UK Clinical Trials Standards (Appendix 3)

1 Introduction, purpose and who should use this SOP

- Standard operating procedures (SOPs) are required to formalize and standardize working practices within departments. They are a useful training tool.
- The purpose of this SOP is to describe how R&D SOPs are prepared, approved, reviewed and implemented.
- This SOP should be used by R&D staff when compiling SOPs. Other departments within the Trust may also find this SOP a useful guide.

2 Preparation and version control

- SOPs will be planned and discussed within the R&D Department in order to agree their content and to resolve any queries during drafting.
- The recommended format of SOPs is to have the following sections; a contents list, introduction, background, purpose, who should use the SOP, details of procedures, acknowledgements, references, appendices.
- The recommended font for SOPs is Arial size 11 with Arial size 9 in Gray-80% in headers and footers.
- Working instruction 01 is a template for SOPs. This is saved on the Y drive in Y:\Research\GCP SOPs & forms\Working instructions.
- Appendix 1 is the list of acronyms and their definitions and is relevant to all R&D GCP SOPs.
- Appendix 2 lists the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted. This applies to all the R&D GCP SOPs.
- SOPs in development will be saved on the Y drive in Y:\Research\GCP SOPs & forms\SOPs and named with the brief title of the SOP and the words 'draft'.
- The words - Draft/date/initials of author - will be kept in the header in the top left hand corner of each page during development of the SOP. For example, Draft/09.09.09/JHP. The date in the header will be up-dated on the day the draft is changed. The title of the SOP will also be in the header above the version details.
- The watermark 'DRAFT' will be added to appear on each page of the SOP.
- Each page will be numbered x of y in the footer starting with the cover as page 1.
- When a draft SOP has been completed as fully as possible, it will be forwarded to either the R&D Manager/QA Manager/R&D Monitor (depending on who the author is) for an in depth review. Comments will be incorporated into the draft SOP.
- When the final draft is reached, the word 'Final' will be added in the header for example, Final draft /09.09.09/JHP and the SOP will be saved with the brief title and the words 'final draft'.

- The final draft of SOPs will be circulated for comments to the rest of the R&D department and members of the R&D Committee.

3 Approval and version control

- R&D Committee members and R&D staff will be given **2 weeks** to feedback any comments to the author.
- If changes need to be made, the amended final version will be forwarded to the R&D Manager, QA Manager and Monitor for a final review and approval.
- Once approved the watermark 'DRAFT' will be removed and SOPs will be given a version number and a date, starting with version 1 and date of approval.
- In the header in the top right hand corner of each page of the SOP will be the title of the SOP and underneath the version details, for example:
  R&D GCP SOP 01 version 1, 23.09.09
- The R&D Director and Manager will then sign off a paper copy of the approved SOPs to authorize the use of the SOPs.
- Original approved signed and dated paper copies of SOPs will be kept in the file labelled SOPs for HEY-sponsored CTIMPs in the R&D Office.

4 Review and up-dating

- SOPs will be assigned a review date 3 years after the approval or previous review date. An automated calendar reminder will be set up to remind R&D when the review date is due.
- SOPs may well require updating before the review date due to a change in legislation or change in MHRA/Ethics/HRA requirements or changes in working practices.
- If the SOP is up-dated the version number and date will be up-dated and the version log will be completed on page 2 of the SOP.
- When the review date is due the author may decide that there is no update required at that time. The author will note in the version log that the SOP was reviewed and required no change and therefore there was no change of version number and date.

5 Dissemination

- SOPs will be placed on the SOP section of the R&D department HEY internet site by the Trust's Web Services department.
- Superseded versions of SOPs will be saved on the Y drive in Y:\Research\GCP SOPs & forms\SOPs.
- A person using a paper copy of an SOP should always check that they have the latest version by checking the R&D internet site. This is stated on the front cover of all SOPs.

6 Training and implementation

- Prior to the start of the study, all research staff involved with the study will be required to read the GCP SOPs and document that they have done so when completing the 'Training method' section of the Training and Delegation Log.
- Likewise, new research staff before becoming involved with the trial, will be required to read the GCP SOPs and document that they have done so when completing the Training and Delegation Log.
- SOPs will be implemented by individual researchers after signing the Training and Delegation Log.
- Departmental training on SOPs will be organized upon request.
- Approximately every 6 months, an email will be sent to research staff informing them of updates to SOPs and asking them by return email to confirm they have read the updated SOPs.
- All returned confirmation emails will be saved in the SOP Up-dates Training Records folder on the Y drive in Y:\Research\GCP SOPs & forms\SOP Up-dates Training Records.
- The R&D monitor will contact any research staff who do not return confirmation emails within a month of receiving the up-dated SOP notification.

Appendix 1 - Acronyms and definitions

A more detailed glossary is available at the Clinical Trials Toolkit website
http://www.ct-toolkit.ac.uk/

AE – Adverse Event: Any untoward medical occurrence in a clinical trial subject administered a medicinal product, medical device or intervention and which does not necessarily have a causal relationship with this treatment.

IB – Investigator Brochure: A document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product. The IB is intended to provide the investigator with information necessary for the safe conduct of the study. The IB is a document of critical importance throughout the drug development process and is updated with new information as it becomes available.

CI – Chief Investigator: The investigator with overall responsibility for the conduct of a multi-site trial. The application for ethical review should be submitted by the CI. The CI is known as the national coordinating investigator on the IRAS application form.

CRFs – Case Report Forms: A printed or electronic document designed to record all of the clinical trial data for each trial subject. Also known as data collection forms. Each subject has a CRF.

CTA – Clinical Trial Authorization: Authorization granted by the MHRA to conduct a clinical study with an IMP.

CTIMPs – Clinical trials which involve investigational medicinal products.

EEA – European Economic Area
EU – European Union

GCP – Good Clinical Practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

HEY – Hull and East Yorkshire Hospitals NHS Trust: Also known as the Trust.

HRA – Health Research Authority: The HRA was established by the Department of Health in December 2011 to promote and protect the interests of patients in health research and to streamline the regulation of research. HRA approval is required prior to the start of a trial.

ICF – Informed Consent Form: A form signed and dated by a study subject which voluntarily confirms their willingness to participate in a study after having been informed of all relevant aspects of the trial.

ICH – International Conference on Harmonization: The objective of ICH GCP is to provide a unified standard for the EU, Japan and USA to facilitate the mutual acceptance of clinical trial data by the regulatory authorities in these jurisdictions.

IMP – Investigational Medicinal Product: An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including products:-
- already with a marketing authorisation but used or assembled (formulated or packaged) in a

way different from the authorised form.
- used for an authorised indication.
- used to gain further information about an authorised form.

ISF – Investigator Site File: A file kept at the PI's site for organizing and collating all trial documents pertaining to the site. The CRFs form part of the ISF.

MHRA – Medicines and Healthcare products Regulatory Agency: The UK authority that reviews clinical research protocols, pharmacovigilance data and medicinal product license applications. This authority also conducts GCP inspections.

PSF - Pharmacy Site File: A trial specific file located in the Pharmacy Department and used to collate the trial documents relevant to pharmacy.

PI – Principal Investigator: The investigator responsible for the clinical trial at the research site. In a multi-site trial, there should be one PI for each research site. In the case of a single-site trial, there is no Chief Investigator just the Principal Investigator.

QA – Quality Assurance refers to the ongoing monitoring and evaluation of the various aspects of a clinical trial to ensure that standards of quality are being met.

REC – NHS Research Ethics Committees consist of up to 18 members, one third are lay members (this means their main professional interest is not in a research area, nor are they a registered healthcare professional). RECs safeguard the rights, safety, dignity and well-being of research participants, independently of research sponsors.
They review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical. RECs are entirely independent of research sponsors, funders and investigators. This enables them to put participants at the centre of their review.

RSI – Reference Safety Information: This is a list of medical events detailing the Serious Adverse Reactions (SARs) that are expected for the IMP which is to be used by investigators as a **reference** point when assessing a SAR to determine whether it is a SUSAR. The documents that contain the RSI are the IB for an IMP without marketing authorisation and an SPC for an IMP with marketing authorisation. Both documents have a section that lists the expected adverse reactions for the IMP.

SAE – Serious Adverse Event: An adverse event is serious if it; results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

SAR – **Serious Adverse Reaction** is a serious adverse event that is either possibly, probably or definitely related to the investigational medicinal product in a study medic's opinion.

SPC – Summary of Product Characteristics.

SUSAR – Suspected Unexpected Serious Adverse Reaction: An SAE becomes a SUSAR if the event is suspected (possibly, probably or definitely) to be related to the IMP and unexpected for i.e. not previously documented in any of the product information (investigator brochure, SPC, patient information leaflet) or protocol.

TMF – Trial Master File: A file, or series of files, either paper or electronic (eTMF), used to collate **all** the trial documents and enables the conduct of a clinical trial and quality of the data produced to

be evaluated by MHRA GCP inspectors. The TMF is the complete history of the trial and will enable the trial to be reconstructed if necessary. The TMF includes the investigator and pharmacy site files as well as the CRFs.

Appendix 2 - UK Clinical Trial Standards

It is a legal requirement for clinical trials that investigate the safety and/or efficacy of a medicinal product, to be conducted according to the UK Clinical Trial Regulations. ICH GCP is incorporated into the UK CT regulations. The UK Framework for Health and Social Care Research must also be followed for the conduct of all research in the NHS.

These are the standards that need to be adhered to for the conduct of CTIMPs sponsored by Hull and East Yorkshire Hospitals NHS Trust in order to protect the safety of clinical trial participants and produce the highest quality clinical trial data.

See below for a summary and weblinks for these documents.

UK CT regulations are available at http://www.legislation.gov.uk/ by entering the Statutory Instrument number.

- Medicines for Human Use (Clinical Trials) Regulations 2004
  Statutory Instrument 2004/1031 (1 May 2004).Transposed European Directive 2001/20/EC into UK law. Known as the **Clinical Trials Directive**
  Implementation of GCP in the conduct of clinical trials on medicinal products for human use
  Ethics review system came under law
  Each member state has to appoint a competent authority (MHRA in UK)
  Additional safety reporting requirements
  Amendments required to follow a process

- Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
  Statutory Instrument 2006/1928 (29 Aug 2006). Transposed European Directive 2005/28/EC into UK law. Known as the **GCP Directive**
  Principles and detailed guidelines for GCP
  Sponsor has overall responsibility – duties can be delegated but not responsibilities
  UK specific requirement to report serious breaches
  Archiving of TMF

- Medicines for Human Use (Clinical Trials) Amendment no. 2 Regulations 2006
  Statutory Instrument 2006/2984 (12 Dec 2006)
  Allows incapacitated adults in certain emergency situations to participate in research without the consent of a legal representative

- Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008
  Statutory Instrument 2008/941 (1 May 2008)
  Allows a minor to receive emergency treatment in clinical trials without parental consent in certain circumstances

- The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009
  Statutory Instrument 2009/1164 (8 May 2009)
  Urgent safety measures – rapid response to public health threats/pandemics e.g. swine flu

- The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010
  Statutory Instrument 2010/1882 (19 Aug 2010)
  Advanced therapy medicinal products – tissue engineered products.

ICH GCP is available at http://ichgcp.net/ (first published in 1996)

- International Conference on Harmonisation Good Clinical Practice (E6)

UK Framework for Health and Social Care Research v3, 10/10/17 is available at https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/