NIHR | King's Clinical Research Facility

Management and Accountability of Investigational Medicinal Products in the King's Clinical Research Facility

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1.0 Background

1.1 An ‘Investigational Medicinal Product’ (IMP) is defined as:

A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,

b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or

c) used to gain further information about the form of that product as authorised under the authorisation. (Clinical Trials Toolkit)

1.2 Current clinical trial legislation details the requirements for the manufacture and importation of IMPs. Under the legislation, clinical trials involving IMPs (CTIMPs) require the IMP to be manufactured according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) should also be adhered to.

1.3 All protocols for CTIMPs should detail the IMP requirements, including a description of the trial treatment, provision of the IMP, labelling, packaging, storage, dispensing, accountability, route of administration, the dosing regimen and any risks and related safety assessments.

2.0 Purpose

2.1 This Standard Operating Procedure (SOP) describes the processes and procedures for the management and accountability of IMPs for trials conducted within the King's Clinical Research Facility (CRF).

3.0 Scope

3.1 The CRF encompasses the Clinical Trials Facility (CTF), the Experimental Medicine Facility (EMF) and the Cell Therapy Unit (CTU). CRF SOPs will apply to the CTF and EMF only and staff working in those areas should work to all relevant CRF SOPs. The CTU will continue to control and use its own policies and SOPs to ensure compliance with Good Manufacturing Practice (GMP).

3.2 This SOP applies to all core CRF staff and users of the CRF who are involved in the management of IMPs within the CRF.

3.3 This SOP focuses on IMP activities which may be undertaken for CTIMPs within the King's CRF and is not an exhaustive operating procedure on all aspects concerning IMPs in clinical trials.

3.4 This SOP will not cover in depth the dispensing of IMPs or pharmacy accountability of IMPs, as these processes fall under the remit of the specific pharmacy departments involved in the trial.

4.0 Responsibilities

4.1 It is the responsibility of the trial Sponsor to have procedures in place to ensure that the manufacturing, packaging, labelling, releasing and distributing of the IMP is conducted according to the principles of Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP), delegating specific responsibilities accordingly.

4.2 The relevant local pharmacy, either King's College Hospital (KCH) or South London and the Maudsley Hospital (SLaM), is responsible for the receipt, storage, accountability, management, return and destruction of IMPs, in accordance with the trial protocol and Sponsor requirements. These responsibilities may be delegated, where appropriate, to another pharmacy or department.

4.3 Responsibility for IMP receipt, storage, administration, accountability and also possibly destruction, may be delegated to the CRF for a particular trial. This may require a trial-specific SOP to be written and approved by appropriate personnel. CRF staff listed on the trial's Delegation Log as having responsibility for any of these procedures are responsible for managing them appropriately, ensuring that all procedures are conducted in accordance with the trial protocol, pharmacy manual (where applicable), relevant SOPs and Sponsor requirements.

4.4 The relevant local pharmacy and the CRF Manager, or appropriate delegate, are responsible for reviewing and agreeing the procedure for the dispensing of the IMP to the CRF clinical staff prior to the commencement of the trial.

5.0 Procedure

IMP distribution and receipt

5.1 When all the required regulatory and local approvals and documentation are in place for the local site, and usually after the site initiation visit (SIV) has been conducted, the IMP will normally be released by the Sponsor of the study to the relevant local pharmacy.

5.2 The Senior Clinical Trials Pharmacist from the relevant pharmacy will be responsible for managing and documenting the receipt of the IMP, code envelopes and randomisation lists, as well as for the storage, dispensing, return and destruction of the IMP for the duration of the study, as agreed with the Sponsor or delegate.

5.3 The Sponsor or delegate should ensure that written procedures are provided to the relevant local Trust pharmacy and CRF, which document the procedures for the handling

and storage of the IMP and include adequate documentation. The procedures should address receipt, handling, storage, dispensing, recall, unblinding, expiry date extensions, temperature excursions, retrieval of unused product from trial subjects, and return of any unused IMP to the relevant pharmacy (or alternative location if authorised by the Sponsor and in compliance with the applicable regulatory requirements).

Dispensing of IMP to CRF staff

5.4 If possible, the IMP should remain in the local hospital pharmacy until the day of administration to the trial participant. However, if required by the trial protocol, or if the IMP is to be administered outside of the pharmacy's working hours, the IMP may be dispensed by the pharmacy to the CRF clinical staff after obtaining the prescription from the Chief Investigator (CI) or Principal Investigator (PI). It must then be stored securely in the CRF and within the specified conditions until preparation and/or administration. The normal working hours of the KCH and SLaM pharmacies are 09.00-17.30hrs, Monday-Friday.

5.5 Upon receipt of a trial subject's IMP, the CRF staff must carefully check that all details on the IMP packaging match that of the prescription (trial ID, dosage, formulation etc). Expiry dates should also be double-checked. Where possible, these details should be checked by two members of clinical staff as delegated.

5.6 Dispensing of any IMP which meets the definition of a controlled drug or substance should comply with the KCH Controlled Drugs Policy.

5.7 All drug dispensing procedures should comply with the KCH Medicines Management Policy.

IMP storage within the CRF

5.8 If an IMP is to be stored within the CRF it must be stored in a secure location appropriate for the defined storage conditions (pharmacy fridge, freezer or appropriate drug cupboard) which is accessible only to CRF staff and appropriate CRF users.

5.9 The temperatures of all CRF fridges and freezers are monitored and recorded 24 hours a day by a web-based temperature monitoring system (as detailed in *CRF-QA-SOP-11: The Tutela Temperature Monitoring System in the King's CRF*). This is to ensure that IMPs are stored within the parameters detailed in the trial protocol and the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB).

5.10 The temperature may need to be recorded for IMPs which are stored in a CRF drug cupboard and this should be done according to the trial-specific instructions in the pharmacy manual and/or protocol.

5.11 If temperature parameters are breached, this must be documented and reported to the CI/PI, Sponsor and pharmacy as soon as possible, and the affected stock quarantined immediately until further instruction is provided by pharmacy and the Sponsor. All quarantined IMP should be labelled clearly as QUARANTINED STOCK and stored in a separate area from any remaining stock. It can be returned to pharmacy if required.

5.12 IMPs which are logged in and out of CRF storage locations (eg: drug cupboard, fridge) must be documented using *CRF-STU-FRM-1: IMP Storage Accountability Log*, unless another form is provided by the Sponsor in which case this form should be used.

5.13 Any IMP which meets the definition of a controlled drug or substance must be stored in the CRF's Controlled Drugs cupboard and recorded in compliance with the KCH Controlled Drugs Policy.

IMP preparation within the CRF

5.14 The Sponsor and the Trials Pharmacy must provide clear, written instructions (in the Pharmacy manual, Study Operations Manual, and/or relevant SOPs) detailing the procedure/s in IMP preparation, including appropriate supplies, dosage calculations, labelling, transport from preparation area to the bedside, and any other relevant instructions such as conditions from storage to preparation, expiry times, guidance on light exposure, etc. These should be reviewed at regular intervals as required.

5.15 CRF staff delegated to prepare the IMP must have had the appropriate training prior to performing trial-related activities. These must be documented in the proper log/s and updated if procedures have been amended.

5.16 In double-blinded CTIMPs, IMP preparation is performed only by the delegated unblinded team in the CTF Pharmacy area or any other designated area. All communication and documentation, including IMP labels and package materials that may otherwise cause accidental unblinding must either be clearly labelled and stored in a designated area, with access restricted to the unblinded team, or destroyed and discarded as per protocol.

5.17 The details of IMP preparation must be documented on the relevant page(s) in the trial's Case Report Form, according to the trial protocol and Sponsor's instructions.

5.18 Any deviation to the IMP preparation procedures must be reported to the CI/PI, pharmacy and Sponsor as soon as the CRF becomes aware of the event. The deviation may also have to be reported to KCH via Datix if it meets the definition of an Adverse Incident (AI), in line with the KHP SOP on Management of Research Incidents and Adverse Events.

IMP administration within the CRF

5.19 The number of subjects dosed for a study within the CRF on any one occasion, and the interval between dosing individual subjects and cohorts of subjects, will depend on the type of IMP, the route of administration and the phase and type of trial.

5.20 The Sponsor must provide clear, written instructions detailing the IMP dosage, dosage frequency, route of administration, frequency of dose escalation (if applicable) and any other relevant instructions such as any other pre-dose assessments and expected adverse drug reactions. These should be reviewed at regular intervals as required.

5.21 IMPs will be administered to trial subjects in the CRF as detailed in the trial protocol, prescription and relevant SOPs. Personnel who are dosing trial subjects must check that subject identifiers, study title, visit number, dose, formulation, frequency, route of administration and quantity of IMP match the prescription. The administration of the IMP to the subject must be documented on the relevant page(s) in the trial's Case Report Form, according to the trial protocol and Sponsor's instructions.

5.22 Additional pre-dose checks to be performed include the presence of patient's ID band, adequately checked and functional resuscitation equipment (e.g. nearest accessible crash trolley, glucometer, oxygen and suction equipment, call bells, etc.), and immediate access to and availability of rescue medications as per protocol.

5.23 Any deviation to the IMP administration procedures for subjects dosed within the CRF must be reported to the CI/PI, pharmacy and Sponsor as soon as the CRF becomes aware of the event. The deviation may also have to be reported to KCH via Datix if it meets the definition of an Adverse Incident (AI), in line with the KHP SOP on Management of Research Incidents and Adverse Events.

5.24 The Sponsor will assess whether or not a serious breach of GCP or of the trial protocol has occurred as a result of a deviation of IMP administration, and, if necessary, will report it to the MHRA within the required timelines.

IMP accountability

5.25 The Sponsor and CI/PI must ensure that responsibility for IMP accountability is clearly stated on the Delegation Log for the trial.

5.26 The relevant local Trust pharmacy will be responsible for maintaining accountability records relating to the delivery of the IMP to the local site, (shipment and receipt dates) inventory at the site, use by each subject, return of unused IMP from subjects and return of unused IMP to the Sponsor or delegated department/organisation. If the CRF is to take responsibility for this, it must be clearly documented in the trial protocol/pharmacy manual and agreed in advance with the CRF Manager, Sponsor and relevant pharmacy.

5.27 Pharmacy accountability records should include the IMP name, strength, form, quantities, batch/serial numbers, expiration dates and the unique code numbers assigned to the investigational product(s) and trial subjects (if applicable), as well as temperature monitoring records which document that the IMP was stored as specified by the Sponsor whilst in the pharmacy.

Emergency Unblinding

5.28 If applicable to the trial, the Sponsor or delegate must have a written procedure in place for rapid unblinding of trial subjects. The procedure must be secure, readily available at all times during the trial, and not allow breaks of the blinding to go undetected.

5.29 CRF staff and users of the CRF must follow instructions detailed in the trial protocol in the event of an emergency situation occurring within the CRF which requires a trial subject to be unblinded.

5.30 No blinded CTIMP trial will be allowed to be conducted within the CRF without robust 24-hour unblinding emergency procedures in place which are agreed by the Sponsor and the relevant local pharmacy.

6.0 Related documents & References

6.1 KCH Controlled Drugs Policy and Medicines Management Policy:

http://kingsdocs/Pages/Home.aspx

6.2 CRF-STU-FRM-1: IMP Storage Accountability Log

6.3 CRF-QA-SOP-5: Safety Reporting and Pharmacovigilance in the King's CRF

6.4 CRF-QA-SOP-11: The Tutela Temperature Monitoring System in the King's CRF

6.5 KHP SOP 23: Management of Research Incidents and Adverse Events, February2020

7.0 List of Appendices

N/A

8.0 Approval and sign off

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