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STU-SOP-TM-012 – Standard Operating Procedure on Management of Medicinal Products used in Research

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Description of changes:	3 yearly review. Updated wording and template.		

1 Abbreviations

CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTP	Clinical Trial Pharmacist
GMP	Good Manufacturing Process
IB	Investigator Brochure
LCTP	Lead Clinical Trial Pharmacist
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
PI	Principal Investigator
QP	Qualified Person
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
SU	Swansea University

Medicinal Product: Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or, any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

It should be noted that medicinal products can be human, animal, vegetable or chemical in origin. A substance may come under both parts of the definition; however, it need only fall under either part of the definition to be classified as a MP.

Investigational Medicinal Product: 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, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Such research projects are classified as Clinical Trials of Investigational Medicinal Products (CTIMPs).

2 Purpose

The purpose of this SOP is to provide information to researchers for the management process of Medicinal Products (MPs) in non-commercial Clinical Trials of Investigational Medicinal Products (CTIMPs) and other research projects conducted at single or multiple research sites.

This SOP does not describe the processes for manufacture or packaging of MP or the release of an Investigational Medicinal Product (IMP) by a Qualified Person (QP), nor the responsibilities of pharmacy departments in dispensing MP for research projects.

This SOP may be used for research projects not adopted by STU where staff in Swansea University (SU) or NHS organisations require guidance on managing MP in a research project.

3 Background

All research projects involving a MP require considerations to be made for the manufacture, management, distribution and accountability of MP. Where such projects are CTIMPs under the Clinical Trial Regulations 2004, there is a legal requirement to receive a clinical trial authorisation (CTA) from the regulatory body in all countries to cover the management of the trial and use of an IMP. The CTA terms ensure the IMP is of sufficient quality and is manufactured and labelled to ensure the safety of the participants and quality of the data.

In addition to the legal requirements there are a number of points for Sponsor and CI to consider during design and set-up of a research project involving MP:

- Confirmation of regulatory, ethical and local R&D approvals are received
- All MP manufacture/assembly/importation activities must be conducted to Good Manufacturing Practice (GMP) by the MP supplier/Marketing Authorisation Holder (MAH) and confirmation of release performed by a Qualified Person (QP)
- An appropriate contract must be in place between the sponsor and any vendor to provide MP and document respective responsibilities, including the quality standards that will be adhered to
- For blinded trials, unless the products are being provided in a final blinded format by the MP supplier/MAH, a process must be agreed for any required manufacturing and assembly activities
- An assessment of all vendors must be performed and documented as in SOP STU-CT008 (Selection and Oversight of Vendors)
- An assessment made to establish the level of MP labelling required as per Annexe 13

4 Roles and Responsibilities

The Sponsor has overall responsibility for MP management. The sponsor may delegate duties to the Chief Investigator (CI) or a vendor.

The **Chief Investigator (CI)** is responsible for liaising with a Clinical Trial Pharmacist (CTP) or equivalent throughout the research project. This action may be delegated to the Trial Manager.

The Principal Investigator (PI) is responsible for the IMP management at their site, although this is often delegated to pharmacy departments.

A **Lead Clinical Trial Pharmacist (LCTP)** or equivalent must be appointed and is responsible for advising on MP storage and handling requirements during the design and oversight of the research project.

A **Clinical Trial Pharmacist (CTP)** or equivalent oversees the receipt and management of MP used in a research project at a site.

The **Trial Manager (TM)** or delegate has responsibility for advising when MP should be released to sites and to oversee the management, distribution and accountability by sites.

5 Procedure

Research Project Set Up

5.1 Project design and protocol development

During drafting of the grant proposal and the risk assessment the CI will convene a Trial Management Group (TMG) and involve a LCTP or equivalent to advise on the use of the MP.

The CI and LCTP shall discuss MP supply, need for an external vendor, or if MP can be sourced from hospital stock; taking into consideration storage requirements for MP and returns.

The CI will establish pharmacy and MP costs and, if required, will obtain an illustrative quote for inclusion with the grant proposal, including arrangements and costs for drug packaging, distribution and randomisation if involved.

The LCTP will review a protocol involving a MP to ensure that all relevant product information and an emergency unblinding mechanism (if required) is included and may be a signatory on the final protocol. Unblinding will be documented in an Emergency Unblinding Form (STU-AD-FRM-012).

The LCTP should review the content of the Participant Information Sheet (PIS) to assess the information supplied to the participant, and the required product information (e.g. Summary of Product Characteristics (SmPC), Investigator Brochure (IB), Simplified Investigational Medicinal Product Dossier (sIMPD), label requirement and text, stability data) for relevance prior to submission for appropriate approvals. STU-AD-TMP-043 provides examples of labels.

The CI, and other parties (as appropriate) will input into the selection of, and contractual arrangements with MP suppliers/manufacturers/distributors, as required.

5.2 MP Ordering, Shipment, Storage and Accountability

The Sponsor or delegate must confirm that all required regulatory approvals and where required, the QP release of MP are in place. This must occur prior to authorising the dispensing of any MP for the research project, as detailed in the Trial Green Light Form (STU-AD-FRM-022) and SOP (STU-CT054).

For ordering externally sourced MP an MP Order Form (STU-AD-FRM-031) should be used. An equivalent sponsor or external vendor order form may be used as appropriate.

For all orders of MP, consideration should be given to MP expiry date and expected recruitment rate in order to identify when multiple orders are required and to minimise wastage.

Advice from a manufacturer or QP should be sought regarding the transportation and temperature monitoring (if required) of MP during transit to pharmacy.

All research projects involving MP require a Pharmacy Site File to be issued by the TM.

In consultation with the LCTP, all project specific templates related to MP shall be developed, including a Site Medicinal Product Accountability Log (STU-AD-TMP-041), Research Project Prescription (STU-AD-TMP-042), emergency Site Unblinding Request Form (STU-AD-FRM-012) and Medicinal Product Request Form (STU-AD-FRM-032).

When a marketed product is used and no trial specific labelling is required, as per Annexe 13 of the Clinical Trials Directive, a justification for the decision will be documented in the trial risk assessment and included in the regulatory application.

MP pharmacy storage areas, including those out with pharmacy, must be locally approved with appropriate processes in place before MP can be sent. If storage of returns out with pharmacy will be undertaken this shall be documented in the protocol and/or the Pharmacy Site File detailing the procedure for recording compliance and return to site pharmacy at appropriate intervals during the project.

5.3 Conduct of research

MP will be released to site on completion of a Site Green Light Form (STU-AD-FRM-022)

Following Sponsor confirmation that all required approvals have been received, MP shall be dispensed on receipt of a signed Research Project Prescription (STU-AD-TMP-042) or transferred to a locally approved storage area, on receipt of a signed Medicinal Product Request Form (STU-AD-FRM-032). Labelling of MP, when required, shall be conducted by pharmacy in accordance with local pharmacy SOPs.

The accountability (including compliance) of MP is the responsibility of all delegated research team members. Project specific requirements will be detailed in the protocol. All dispensing/return of MP shall be recorded in medical records, Case Report Forms (CRF) and a Site Medicinal Product Accountability Log (STU-AD-TMP-041)

Temperature logging and temperature deviations of MP stored within pharmacy will be managed by pharmacy in accordance with local SOPs. The trial office and Sponsor must be informed of any temperature excursions as soon as pharmacy become aware. The CI/TM shall liaise with a LCTP or manufacturer to advise on a required correction and any corrective and preventive action (CAPA).

Expiry management and relabelling, where required, shall usually be conducted by the local pharmacy in accordance with pharmacy SOPs.

For randomised research projects, arrangements shall be in place for emergency unblinding, detailed in the protocol and documented via a Site Unblinding Request Form (STU-AD-FRM-012). In exceptional circumstances, the site CTP may need to be involved in out of hours unblinding. The site CTP shall be consulted on all unblinding procedures.

MP recall, where required, shall be conducted by the local pharmacy and trial office in accordance with the protocol and pharmacy SOPs.

A LCTP will be consulted during drafting of any amendment which affects management of the MP or involves the addition of an investigational site which will require supply of MP. Site CTPs will be given copies of all documents relating to relevant amendments to the research project for information and for filing in the Pharmacy file.

In exceptional circumstances, MP transfer to another investigational site, where needed, shall be conducted by the LCTP and TM in accordance with the Sponsor's SOPs.

All MP and/or packaging returned to site e.g., routine returns, withdrawals, recalls etc. must be documented in a Local Medicinal Product Accountability Log (STU-AD-TMP-041). Once recorded, all MP shall be returned to the local pharmacy for accountability and destruction. This will be done in accordance with local pharmacy SOPs, unless otherwise notified in the protocol.

6.4 Close-out

Once recruitment and any follow up is completed, the research team will inform the site CTP that the project is complete, and that the pharmacy file can be archived. The pharmacy file will be reconciled, and all documentation completed and accounted for. Any unblinding documentation shall remain in the pharmacy file unless requested by the CI for inclusion in the TMF.

The site CTP will reconcile all remaining MP. Any remaining MP that had been stored outside pharmacy must have been returned for destruction along with a copy of the completed Local Medicinal Product Accountability Log (STU-AD-TMP-041). The site CTP will ensure that pharmacy accountability logs are reconciled, completed and signed off. MP shall be destroyed as per pharmacy SOPs. A local destruction form shall be completed and signed off by the site CTP.

The pharmacy file should be archived with the TMF.

6 References

- Health Research Authority website (HRA) - http://www.hra.nhs.uk/
- Medicine and Healthcare products Regulatory Agency website (MHRA) - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/services-information
- UK policy framework for health and social care research (2017) - **Error! Hyperlink reference not valid.**https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/
- UK Medicine for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made
- Directive 2001/20/EC Article 13/14; European Commission Clinical Trials– https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
- Directive 2001/83/EC relating to Medicinal Products for Human Use - http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf
- The Human Medicines Regulations 2012/1916 - http://www.legislation.gov.uk/uksi/2012/1916/pdfs/uksi_20121916_en.pdf
- Annexe 13, Detailed guideline on GMP for IMP - https://ec.europa.eu/health/documents/eudralex/vol-4_en

It is assumed that by referencing the principal regulations that all subsequent amendments are included in this citation.

7 Associated Documents

Number	Title	Location
STU-AD-FRM-012	Emergency Site Unblinding Form	Q-Pulse
STU-AD-TMP-043	Example IMP Label Form	Q-Pulse
STU-AD-FRM-022	Regulatory Green Light Form	Q-Pulse
STU-AD-FRM-031	Medicinal Product Order Form	Q-Pulse
STU-AD-TMP-041	Local Medicinal Product Accountability Log	Q-Pulse
STU-AD-TMP-042	Research Project Prescription	Q-Pulse
STU-AD-FRM-032	Medicinal Product Request Form	Q-Pulse

8 Appendices

None required for this SOP