STANDARD OPERATING PROCEDURE FOR MANAGEMENT OF CLINICAL TRIAL MEDICINES

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1. PURPOSE

This document describes the role of the pharmacy service in relation to Clinical Trials of an Investigational Medicinal Product (CTIMPs) in NHS Fife and complies with the principles of Good Clinical Practice (GCP).

It is the responsibility of all staff using this SOP to ensure they are using the latest version of it. The latest version is available via the Research & Development (R&D) pages on the NHS Fife Intranet (www.nhsfife.org/research). For guidance, contact the R&D Department via fife-uhb.randd@nhs.net

2. APPLICABILITY

This SOP applies to pharmacy staff and all research personnel involved in CTIMPs in NHS Fife including Chief Investigators (CIs), Principal Investigators (PIs) and Research nurses.

3. POLICY

3.1 The role of the pharmacy service in relation to CTIMPs is to safeguard the patients, healthcare professionals and NHS Fife by ensuring that any Investigational Medicinal Product (IMP) used is appropriate for use and procured, handled, stored, used safely and correctly and disposed of appropriately.

3.2 The Medicines for Human Use (Clinical Trials) Regulations 2004 imposed legal standards on the conduct of all CTIMPs and pharmacy must ensure that procedures are in place to comply with the Regulations, relevant Guidelines and Directives.

3.3 The management of IMPs must comply with the Medicines For Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments and all relevant NHS Fife policies.

3.4 All IMPs used within NHS Fife should be stored, dispensed and managed to the same standards as other medicines used therapeutically.

3.5 For the majority of CTIMPs run within NHS Fife, IMP will be stored within pharmacy and dispensed to trial patients on receipt of a prescription (see section 4.5.6.1). However, in exceptional circumstances for some trials it may be necessary for the Investigator to hold stock of IMP outside of pharmacy (see sections 4.5.6.2 and 4.5.6.3).

3.6 IMP can only be stored outside pharmacy following assessment and approval of the proposed storage area by the Clinical Trials Pharmacy Team (See SOP CTP018 - Procedure for Carrying out a Pharmacy Check of IMP that is to be Stored and

Dispensed by the Investigator) and review and approval as part of the Local Management Approval process.

3.7 The storage of IMP outside of pharmacy must also be agreed by the trial Sponsor.

3.8 All IMP must be received through the Pharmacy Department prior to issue to the PI or delegate for storage in the agreed area.

3.9 IMP must only be used for patients recruited to the trial.

4. PROCEDURE

4.1 Registration of New Trials

For all CTIMPs, the Clinical Trials Pharmacy Team must made aware of the potential trial at the site selection stage and supplied with a copy of the protocol and Investigator's Brochure (IB) as soon as these are available. It is the Investigator's responsibility to keep the Clinical Trials Pharmacy Team informed as to how the set-up of the trial is progressing. Documentation for potential trials will be kept for 12 months from the anticipated start date. Thereafter this will be destroyed, after checking with the R&D Office, if there has been no communication from the Investigator.

4.2 Pharmacy Review of CTIMPs

4.2.1 Pharmacy review of CTIMPs forms an integral part of the NHS Fife Local Management Review process.

4.2.2 This review is conducted by the Senior Clinical Trials Pharmacist (See CTPSOP 10 - Review and Set up of a Clinical Trial) and a minimum of two weeks is required from receipt of the protocol for pharmacy to conduct the review.

4.2.3 The Clinical Trials Pharmacy Team will liaise with the Investigator to resolve any IMP related queries and if necessary will contact the Sponsor directly in order to expedite pharmacy internal processes.

4.2.4 The Clinical Trials Pharmacy Team must make the research team and NHS Fife R&D Approvals Team aware of any potential issues and confirm that these have been resolved prior to Local Management Approval being issued.

4.3 Investigator Responsibilities During Approval and Initiation of CTIMPs

4.3.1 The PI must ensure an Initiation Meeting is held between the Sponsor and/or member of the research team and the Clinical Trials Pharmacy Team, usually after the trial has been approved by R&D, to discuss the practicalities of dispensing and other pharmacy support required during the trial. A minimum of 2 weeks notice is required before this Initiation Meeting.

4.3.2 The PI must ensure that pharmacy is aware of the arrangements for emergency unblinding that have been made with the Sponsor. The PI must also provide pharmacy with Out of Hours contact details for the research team and code break information if applicable, as per R&D SOP39.

4.3.3 The PI and study team must contribute to the development of the dispensing procedure for their trial. This will include reviewing and approving study specific prescriptions drafted by the Clinical Trials Pharmacy Team.

4.3.4 The PI must ensure that all prescribers have received appropriate trial specific training and have signed the relevant section of the trial delegation log. The PI must provide pharmacy with a copy of the completed delegation log detailing all personnel able to prescribe for each trial.

4.3.5 The PI must obtain written confirmation from the Senior Clinical Trials Pharmacist that they are ready to start dispensing before the first patient is seen.

4.3.6 The PI must inform patients that the dispensing process for clinical trial prescriptions takes longer than normal prescriptions due to the completion of trial specific paperwork. Where possible, prescriptions should be presented in advance so that patient waiting times may be minimised.

4.3.7 The PI must provide information to trial patients on how study medication should be administered.

4.3.8 The PI must provide the Clinical Trials Pharmacy Team with an updated IB or alternative reference safety information whenever this is updated.

4.4 Pharmacy Responsibilities During Approval and Initiation of Clinical Trials Involving IMP

4.4.1 The Senior Clinical Trials Pharmacist will have overall responsibility for the Clinical Trials Pharmacy service, liaising with the Senior Clinical Pharmacist for the relevant area.

4.4.2 The Senior Clinical Pharmacist for the relevant area must review the protocol in line with CTPSOP 09 - Clinical Trial Review by Clinical Pharmacist.

4.4.3 The Clinical Trials Pharmacy Team will carry out risk assessments, in collaboration with the Investigator, for each CTIMP and put procedures in place to minimise the predictable risks from the IMP to patients and staff (See CTPSOP 10 - Review and Set up of a Clinical Trial).

4.4.4 The Clinical Trials Pharmacy Team will ensure that all IMPs provided or procured for use in trials are manufactured in accordance with Good Manufacturing Practice by a holder of a manufacturing authorisation for IMP, are of suitable quality and fit for purpose.

4.4.5 The Clinical Trials Pharmacy Team will ensure that the packaging and labelling of IMP are acceptable for use within NHS Fife and comply with applicable legislation (Annex 13 Manufacture of Investigational Medicinal Products. Eudralex Volume 4. Good Manufacturing Practices July 2010). Additional labels will be prepared by the Clinical Trials Pharmacy Team where required and will comply with applicable legislation.

4.4.6 Pharmacy charges detailed in the Clinical Trials Agreement with the Sponsor must be reviewed by the R&D Business Accountant in conjunction with the Senior Clinical Trials Pharmacist as part of the Local Management Approval process.

4.4.7 Before dispensing of IMP can begin the Clinical Trials Pharmacy Team must ensure that the necessary approvals are in place (see CTPSOP 10 - Review and Set up of a Clinical Trial).

4.4.8 A member of the Clinical Trials Pharmacy Team will attend either the main Site Initiation Meeting (SIV) or a pharmacy specific Initiation Meeting with the Sponsor's representative and/or a member of the local trial team.

4.4.9 Following the SIV a trial specific dispensing procedure will be prepared as appropriate (See CTPSOP 10 - Review and Set up of a Clinical Trial and CTPSOP 11 - Clinical Trial Pharmacy Instructions).

4.4.10 At least two weeks is required between the Initiation Meeting and the first patient dispensing. This will allow time for the dispensing procedure to be written and for staff training. This timeframe should be confirmed with the Clinical Trials Pharmacy Team during the SIV, as in certain circumstances a longer timeframe may be required.

4.4.11 All pharmacy staff must ensure they complete all appropriate in-house and study specific training prior to undertaking any tasks within a clinical trial (see Section 5).

4.5 Responsibility For IMP Management During Active Trials

4.5.1 The CI/PI has overall responsibility for providing 24 hour emergency contact and unblinding procedures, drug accountability and monitoring compliance for the duration of the trial.

4.5.2 All pharmacy procedures will be carried out in accordance with current NHS Fife Clinical Trial Pharmacy SOPs.

4.5.3 Pharmacy will provide facilities for emergency contact and unblinding 24 hours a day, according to procedures agreed with the CI/PI. R&D SOP 39 - Arranging and Testing 24 Hour Medical Cover For CTIMPs and CTPSOP 6 - Procedure for Emergency Contact and Unblinding should be followed by the CI/PI and pharmacy personnel.

4.5.4 Pharmacy will ensure the correct receipt and recording of deliveries by a responsible person (see CTPSOP 01 - Receipt of Clinical Trial Material).

4.5.5 Pharmacy will ensure reconciliation of delivery records with usage and return of unused stock.

4.5.6 The IMP management process will vary according to where the IMP is stored.

4.5.6.1 <u>All IMP held in Pharmacy</u>

The Clinical Trials Pharmacy Team will be delegated the following duties:

- Maintenance of the dedicated room(s) or storage location(s) for IMPs within pharmacy. These will be temperature-controlled, secure locations with access restricted to pharmacy staff only. All IMP storage locations within pharmacy will have temperatures monitored and recorded in compliance with Good Clinical Practice (See CTPSOP 07 –Clinical Trials Storage Area Monitoring).

- Dispensing IMP against an appropriate prescription following trial specific dispensing procedures (see CTPSOP 02 – Dispensing and Checking a Clinical Trial).

- Preparation of a trial–specific prescription template for approval by the local research team if one has not been provided by the Sponsor.

- Maintenance of accurate accountability records for all IMP.

- Ensuring that the blind is maintained throughout the trial and if applicable, code break envelopes or codes are returned to the Sponsor or Investigator at the end of the trial. Code break envelopes or randomisation lists will only be returned to the Sponsor (or CI) when written evidence from the Sponsor has been provided to the Senior Clinical Trials Pharmacist that the final locked dataset has been verified.

- Appropriate storage of all IMP returned by patients during a trial within the pharmacy, separate from IMP to be dispensed. Commercial companies acting as Sponsor are responsible for disposal of all returned IMP and unused IMP unless otherwise specified in the Clinical Trials Agreement. Where required, disposal of IMP may be arranged with pharmacy (See CTPSOP 08- Clinical Trial Material Destruction and Waste Disposal).

- Provision of appropriate facilities for trial monitoring and access to the trial specific Pharmacy File, IMP supplies and returns. Appointments for monitoring or any other trial related visits to the Pharmacy Department must be made with the Clinical Trials Team with a minimum of 2 weeks notice given.

4.5.6.2 IMP held in the Pharmacy Department with Limited Stock Supplied to PI

- The Pharmacy Clinical Trials Team will be delegated the duty of management of IMP held in the Pharmacy Department outlined in Section 4.5.6.1.

- The PI will be responsible for the appropriate storage, temperature monitoring and accountability of IMP held outside of pharmacy (see R&D SOP43 - Temperature Monitoring of Investigational Medicinal Products Stored Outside Pharmacy). The Clinical Trials Pharmacy Team can provide advice about suitable storage areas, temperature monitoring and accountability processes.

- Following initial approval by the Clinical Trials Pharmacy Team, the Sponsor must take responsibility for the ongoing review of PI storage facilities, drug accountability and monitoring records during the course of the trial.

- In the event of a recall of the IMP by the Sponsor (or IMP manufacturer) the Clinical Trials Pharmacy Team must follow CTPSOP 17 - Procedure for Handling Product Recalls of Clinical Trial Investigational Medicinal Products or Other Trial Related Drugs and contact the PI to inform them that the IMP must be returned to the Clinical Trials Pharmacy Team. The recalled IMP must be quarantined in the Pharmacy Department until further instructions are received from the Sponsor.

- Before the IMP is due to expire (timing is study specific) the Clinical Trials Pharmacy Team will contact the PI (or delegate) to arrange timely return of expiring IMP and arrange a resupply. The expiring IMP will be stored in the Clinical Trials Pharmacy returns area until permission for destruction is received from the Sponsor.

4.5.6.3 <u>All IMP held and dispensed by PI</u>

- The Clinical Trials Pharmacy Team can provide advice about suitable storage areas, temperature monitoring and accountability processes.

- The PI must ensure compliance with the following duties (usually delegated to pharmacy):

    - Proper safe handling, storage, dispensing of IMP (see R&D SOP43 - Temperature Monitoring of Investigational Medicinal Products Stored Outside Pharmacy). The Clinical Trials Pharmacy Team can provide advice about suitable storage areas, temperature monitoring and accountability processes.

    - Issuing of IMP against an appropriate prescription

    - Maintain accurate drug accountability records.

    - Return of unused IMP to pharmacy

    - Safe keeping of randomisation code envelopes and the provision of 24 hour cover to access the code-break.

    - Archiving of IMP related documentation.

- Following initial review and approval by the Clinical Trials Pharmacy Team, the Sponsor must take responsibility for the review of PI storage facilities, drug accountability and monitoring records during the course of the trial.

5. TRAINING

5.1 The Clinical Trials Pharmacy Team must undertake two yearly Transcelerate accredited GCP training.

5.2 The Clinical Trials Pharmacy Team deliver biennial in-house training sessions for the wider Pharmacy team which includes GCP awareness. These sessions are tailored to the wider Pharmacy team's level of input into clinical trials. All staff involved with the day to day management of a clinical trial and/or dispensing of IMP must receive this training.

5.3 All staff must read the trial specific dispensing procedure prior to working on a trial, and again during the course of the trial if updates are made to the dispensing procedure.

5.4 For the Clinical Trials Pharmacy Team and all staff listed on a trial delegation log, evidence of GCP training must be filed in the Investigator Site File and Pharmacy File.

5.5 For staff in the wider Pharmacy team, evidence of in-house training must be filed within the Pharmacy Department.

6. ASSOCIATED DOCUMENTS

CTPSOP 01 - Receipt of Clinical Trial Material
CTPSOP 02 - Dispensing and Checking a Clinical Trial
CTPSOP 06 - Procedure for Emergency Contact and Unblinding
CTPSOP 07 - Clinical Trials Storage Area Monitoring
CTPSOP 08 - Clinical Trial Material Destruction and Waste Disposal
CTPSOP 09 - Clinical Trial Review by Clinical Pharmacist
CTPSOP 10 - Review and Set up of a Clinical Trial
CTPSOP 11 - Clinical Trial Pharmacy Instructions
CTPSOP 17 - Procedure for Handling Product Recalls of Clinical Trial Investigational Medicinal Products or Other Trial Related Drugs
CTPSOP 18 - Procedure for Carrying Out a Pharmacy Check of IMP that is to be Stored and Dispensed by the Investigator
R&D SOP39 - Arranging and Testing 24 Hour Medical Cover for CTIMPs
R&D SOP43 - Temperature Monitoring of Investigational Medicinal Products Stored Outside Pharmacy

7. DEFINITIONS / ABBREVIATIONS

CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
GCP	Good Clinical Practice
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research and Development
SIV	Site Initiation Visit

SOP Standard Operating Procedure

8. REFERENCES

Medicines for Human Use (Clinical Trials) Regulations 2004.
(*http://www.opsi.gov.uk/si/si2004/20041031.htm*).
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

Annex 13 Manufacture of Investigational Medicinal Products. Eudralex Volume 4. Good Manufacturing Practices July 2010

9. DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of Revisions Made:
1	Julie Aitken R&D Trials Facilitator	02 Feb 2015	N/A – new SOP
2	Julie Aitken R&D Trials Facilitator	08 Jun 2016	Amended to reflect current practice
3	Jennifer Tait Senior Clinical Trials Pharmacist	25 May 2020	Reformatted in line with current SOP template. Procedures related to NHS Fife Sponsored trials deleted. Names of associated SOPs updated.

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	11 May 2020