Reference Number: UHB 040 **Version Number: 3**	**Date of Next Review: 26 Apr 2019** **Previous Trust/LHB Reference Number: T 363**

Investigational Medicinal Product (IMP) Management
Standard Operating Procedure

Introduction and Aim
This procedure is written to support the Research Governance Policy.
The aim is to inform the Sponsors and Investigators of the role of pharmacy in the approval and management of IMPs for clinical trial use within the health board.

Objectives
To inform Sponsors and Investigators of pharmacy requirements for the safe management of IMPs approved by the UHB.
To define and clarify the role of pharmacy and its responsibilities with regard to the review of clinical trials and the management of IMPs within Cardiff and Vale UHB.

Scope
This procedure applies to all of our staff in all locations including those with honorary contracts working within the field of clinical trials.

Equality Impact Assessment	An Equality Impact Assessment has been completed. (The Equality Impact Assessment completed for the policy found there to be no impact.)
Health Impact Assessment	A Health Impact Assessment (HIA) has not been completed as it has no impact.
Documents to read alongside this Procedure	Research Governance Framework for Health and Social Care in Wales 2nd Edition 2009. Research Governance Policy (UHB 099). R&D related standard operating procedures of relevance to the reader.
Approved by	Research Governance Group.

Accountable Executive or Clinical Board Director	Medical Director
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Summary of reviews/amendments			
Version Number	**Date of Review**	**Date Published**	**Summary of Amendments**

	Approved		
1	*October 2010*	25th March 2011	Replacement of trust version 363 to UHB040.
2	September 2015		The document has been transferred to the UHB corporate template.
3	26 April 2016	04 Aug 2016	The document has been re-formatted and the layout amended to improve its presentation. A list of sections has been introduced. Section 3 The content of the section remains largely unchanged. Roles and responsibilities have been specified to Sponsor, Investigator and Pharmacy. Duplicated information has been removed. Additional section 'UHB Chief Investigators considering CTIMPs for which UHB is Sponsor Section 4 This section remains largely unchanged, duplicated information has been removed. Phrasing has been made more concise. Section 7 introduction of Incidents and Errors. Section 8 (previously section 7 implementation). Section 9 (previously section 8 Equality Impact and Assessment). Section 10 - Introduction of Audit. Section 11 - previously section 10 distribution. Distribution has been amended to via the UHB Intranet. Section 12 The title has been changed to information sources and the references have been removed from the text but the reference sources used have been listed. The pharmacy R&D form has been removed as a new Support in Principle form is being used by R&D and supported by pharmacy.

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SECTION 1. INTRODUCTION

The role of the pharmacy service in relation to clinical trials is to safeguard the patients, healthcare professionals and Cardiff and Vale University Health Board (UHB) by ensuring that any Investigational Medicinal Product (IMP) used in a trial is appropriate for use and procured, handled, stored, used safely and correctly and disposed of appropriately.

In May 2004 the Medicines for Human Use (Clinical Trials) Regulations came into force. These impose legal standards on the conduct of all interventional clinical trials involving medicines. Pharmacy must ensure that procedures are in place to comply with the regulations and relevant guidelines and directives e.g. Good Clinical Practice (GCP) for clinical trials

The use of medicines in interventional trials must be covered by a Clinical Trial Authorisation (CTA) issued by the Medicines and Healthcare products Regulatory Agency (MHRA). Whilst some clinical trials will involve the use of existing marketed products used within their licensed indications, others will use new medicines, formulations or methods of administration unfamiliar to staff handling them. The clinical trial medicines may also be coded to prevent ready identification by investigator or patient. Extra precautions need to be taken to ensure safety and security in their use.

This procedure sets out the standards required for IMP management within C&V UHB. It applies to all interventional trials involving medicines (excluding wound dressings and blood products). This encompasses all phases of clinical trials from Phase 1 human volunteer studies to Phase IV post-marketing studies. These may be non-commercial (including investigator-initiated) or commercial trials.

SECTION 2. OVERARCHING STATEMENT

The management of clinical trial medicines must comply with legislation and all relevant C&V UHB Research and Development policies.

All medicines used in clinical trials within C&V UHB should be stored and dispensed by the Pharmacy department and managed to the same standards as other medicines used therapeutically. IMP must not be stored in offices, clinics or ward areas unless by prior arrangement with pharmacy and only where appropriate risk management processes and standard operating procedures (SOPs) are in place as outlined in this procedure.
IMP must only be used in patients recruited to the trial.

SECTION 3. RESPONSIBILITIES OF THE SPONSOR, INVESTIGATOR AND PHARMACY DURING STUDY SET UP

3.1 Sponsor/Investigator responsibility (or person(s) with delegated duty to act) with regards the registration of new trials involving IMPs and their role during the approval and initiation process.

- For all trials involving an IMP a copy of the protocol and any documents relevant to pharmacy (e.g. pharmacy manual) must be submitted to the Pharmacy clinical trials team based at UHW at the same time that the trial is registered with R&D.

- All clinical trials involving IMPs are governance reviewed by the Cardiff and Vale Research Review Service (CaRRS).
- All clinical trials involving IMPs that are sponsored by Cardiff University or Cardiff and Vale UHB, are also reviewed by the pharmacy clinical trials team as part of the sponsored assessment process (SAP) .

- Pharmacy must be kept informed regarding the trial progression before it is officially submitted for review via CaRRS. Protocols will be kept for 6 months from the anticipated start date. They will then be destroyed if there has been no communication from the investigator.

- The sponsor should provide copies of approvals to the pharmacy clinical trials team before a clinical trial involving medicines can commence (Research Ethics Committee, Medicines and Healthcare Products Regulatory Agency (MHRA), UHB Research and Development Department).

- For non-commercial trials obtain a quote for any pharmacy research costs including funding for excess treatment costs where applicable.

- An initiation meeting must be held between the sponsor and a member of the clinical trial pharmacy team.

- Confirmation must be agreed with pharmacy regarding the arrangements for emergency unblinding.

- Confirm with the pharmacy clinical trials team that pharmacy are ready to start the trial before the first patient is seen.

- Supply pharmacy with a copy of the completed delegation log.

- Provide pharmacy with an updated Investigators Brochure (IB) or SmPC on an annual basis, or every time it is updated, whichever is sooner.

- Inform pharmacy when the trial has been completed and is ready for close down.

3.2 UHB Chief Investigators considering CTIMPs for which UHB is sponsor

- CI should contact the pharmacy clinical trials team (clinicaltrials.pharmacy.cav@wales.nhs.uk) with details of the trial proposal and the IMP involved. A clinical trials pharmacist reviews the information and liaises with the appropriate directorate pharmacist in order to establish the feasibility of the trial prior to submission to R&D for review.

- The CI should liaise with pharmacy whilst developing the protocol to ensure all relevant IMP information is included.

If the trial is deemed feasible pharmacy clinical trial team will provide advice and support to the CI and reviewthe relevant sections of the protocol

- Where there is confusion regarding whether a trial is a CTIMP or not, pharmacy will contact the MHRA clinical trials helpline to establish this.

3.3 Pharmacy responsibility regarding the peer review of clinical trials involving IMP

Pharmacy review of clinical trials involving IMP forms an integral part of the UHB R&D review process.

- This review is conducted by the directorate (or other specialist) pharmacists and the clinical trials pharmacist.

- Wherever possible, the clinical trials pharmacist will liaise with the investigator/sponsor to address any IMP issues prior to consideration by CaRRS.

- Comments from pharmacy reviewers will be submitted to R&D for CaRRS governance review within 10 days of it being received from R&D.

- The pharmacy clinical trial team is represented on the CaRRS panel.

3.4 Pharmacy responsibilities during approval and initiation of clinical trials involving IMPs

- The clinical trials pharmacist will carry out risk assessments, in collaboration with the investigator, for each clinical trial and put procedures in place to minimise therisk and safeguard patients and staff.

- Members of the pharmacy clinical trials team will ensure that all clinical trial medicines provided or procured for use in trials are manufactured and labelled in accordance with Good Manufacturing Practice for IMPs.

- Commercial trials will be assigned a cost based on the National Institute for Health Research, Clinical Research Network, Industry Costing Template and will be agreed between the Sponsor, pharmacy and R&D. The approved pharmacy charges will be included in the UHB Clinical Trials Agreement with the Sponsor.

- Following the pharmacy clinical trials team initiation meeting a trial specific dispensing procedure will be prepared.

- At *least two weeks* is required between the initiation meeting and the first patient dispensing, but pharmacy aim to reduce this time period where possible.

- All staff involved with the day to day dispensing and management of a clinical trial will receive in-house training.

SECTION 4. Responsibility for IMP management during active trials and following trial discontinuation and closedown.

For the majority of clinical trials run within Cardiff and Vale UHB all trial IMPs will be stored within pharmacy.

However, in exceptional circumstances for some trials it may be necessary for the investigator to hold a small stock of IMP outside of pharmacy. If the need for storage of IMP outside of pharmacy is identified during the protocol review the clinical trials pharmacist will highlight this in the CaRRS report. The storage of IMP outside of pharmacy needs to be approved by the CaRRS panel.

In very exceptional circumstances, the Clinical Trials Pharmacist, Principal Investigator (PI) and CaRRS panel may decide that it is more appropriate for all the IMP management to be performed by the PI with no pharmacy involvement (see section 4.3).

The IMP management process will vary according to where the IMP is stored. If the trial is Sponsored by an external organisation the storage of IMP outside of pharmacy will need to be agreed by the Sponsor as well as CaRRS.

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4.1 All IMP held in pharmacy

The pharmacy clinical trials team will be responsible for:

- Correct receipt and recording of deliveries by a responsible person.
- Maintenance of the dedicated temperature controlled secure rooms or storage locations for clinical trials within pharmacy.
- Dispensing IMP against an appropriate prescription following trial specific dispensing procedure.
- Maintenance of accurate accountability records for all IMP.
- Reconciliation of IMP received, stored and dispensed in pharmacy including patient returns. The level of support may vary between trials.
- Ensuring that the blind is maintained throughout the trial and 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 released to the trial sponsor (or investigator) when written evidence from the sponsor has been provided to the clinical trials pharmacist that the final locked dataset has been verified.
- Emergency un blinding supported by pharmacy, according to an agreed procedure.
- Provision of appropriate facilities for trial monitoring by pre-arranged appointments.

4.2. IMP held in pharmacy with small stock supplied to PI

- The pharmacy clinical trials team will retain responsibility for the IMP held in pharmacy as outlined above.
- Pharmacy will keep up to date details of any IMP held outside pharmacy.
- The PI will be responsible for the appropriate storage, temperature monitoring and accountability of IMP held outside of pharmacy. This may include procuring new equipment. Pharmacy staff can provide advice about suitable storage areas, temperature monitoring and accountability processes and assist the PI in preparing the relevant procedures.
- Before full CaRRS approval is granted, UHB clinical trials pharmacist will inspect the PI facilities for storing IMP and the relevant procedures will be approved by Pharmacy.
- The Pharmacy clinical trials team will perform a trial monitoring visit of the IMP storage and accountability three months after the trial starts. Items to be monitored are:
    - ❖ Storage conditions of IMP including temperature monitoring records
    - ❖ Balance of IMP held by PI

- ❖ Adequate completion of accountability records

- R&D will be informed of the results of the monitoring visit and any deficiencies will be reported to RGG by the pharmacy representative attending.

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- The frequency of future monitoring will be based on the results of the first monitoring visit.

- If the trial is sponsored by an external organisation (e.g. pharmaceutical company) the sponsor may take responsibility for inspecting the PI storage facilities before the trial starts and also routinely inspect storage facilities, drug accountability and monitoring records during the course of the trial.

- If the temperature in the PI storage area goes outside the approved range the PI must return all stock to pharmacy. The pharmacy clinical trials team will follow an internal procedure and quarantine the stock until further information is obtained from the trial sponsor. New stock will not be released by pharmacy until the temperature has returned within the acceptable range.

- In the event of a recall of the IMP by the trial sponsor, the pharmacy clinical trials team will follow an internal procedure and inform the PI that the IMP must be returned to pharmacy.

- Before the IMP is due to expire the pharmacy clinical trials team will contact the PI (or delegate) to arrange timely return of expiring IMP and resupply. The expiring IMP will be stored in the clinical trials returns section until permission for destruction is granted by the trial sponsor.

4.3. All IMP held by PI with no pharmacy involvement

- In this case the PI has taken overall responsibility for drug accountability. This will be documented on the site delegation log.

- Duties may include:-
  - ❖ Correct receipt and recording of deliveries by a responsible person.
  - ❖ Proper safe handling, storage, dispensing.
  - ❖ Ensure all IMPs are packaged and labelled according to GMP requirements and regulations, and are legible and understandable to patient/carer.
  - ❖ Issue against an appropriate prescription.
  - ❖ Maintain drug accountability records.
  - ❖ Reconciliation of delivery records with usage and return of unused stock.
  - ❖ Safe storage of used and returned IMP before dispatch to external sponsor for disposal.
  - ❖ Safe keeping of randomisation code envelopes and the provision of 24 hour cover to access the code-break.
  - ❖ Archiving of clinical trial documentation.

- Pharmacy staff can provide advice about suitable storage areas, temperature monitoring and accountability processes and assist the PI in preparing the relevant procedures.

- Before full CaRRS approval is granted either the trial Sponsor or UHB Pharmacy staff will inspect the PI facilities for storing IMP and approve the relevant procedures.

- Ongoing IMP monitoring arrangements during the trial will be agreed with the trial Sponsor.

- If the Sponsor or another external organisation (e.g. CRO) is not monitoring IMP on a regular basis the pharmacy clinical trials team will perform a trial monitoring visit of the PI IMP storage and accountability three months after the trial starts as detailed in pharmacy internal workplace instructions.

4.4 Trial discontinuation and closedown

The Sponsor or their delegate will inform pharmacy when a trial has been discontinued and requires closedown.

Pharmacy will follow their internal procedure to ensure this process is completed.

The process will include:-
Disposal of IMP
Archiving of study file
Anonymising of patient details where appropriate
Checklist of documentation
Inform R&D when close down is complete.

SECTION 5. RESOURCES

This procedure provides advice and information for staff. It is therefore unlikely that any additional resource will be required.

SECTION 6. TRAINING

Appropriate training for staff involved in clinical trials is provided by the UHB through GCP seminars including pharmacy led seminars covering IMP management. Pharmacy staff will receive training as deemed appropriate through the Personal Development Review process.

SECTION 7. INCIDENTS AND ERRORS

All incidents and errors which affect the quality of the IMP or patient safety will be investigated in accordance with Pharmacy internal procedures and reviewed by the Research Governance Group.

SECTION 8. IMPLEMENTATION

The Pharmacy Clinical Trials Group, Research Governance Group and CaRRS will endeavour to ensure that this procedure is implemented. This will be re-enforced within Clinical Boards by local clinical governance arrangements.

SECTION 9. EQUALITY IMPACT AND ASSESSMENT

This procedure has had an equality impact assessment which has shown that there should be no adverse effect on or discrimination against any particular individual or group.

SECTION 10. AUDIT

It will be necessary to ensure compliance to the requirements of this procedure. Audit of compliance against the guideline and GCPs can be undertaken periodically by internal and external inspectors as applicable.

SECTION 11. DISTRIBUTION

This procedure will be available on the Pharmacy and R&D UHB Intranet.

SECTION 12. INFORMATION SOURCES

1. Professional Guidance on Pharmacy Services for Clinical Trials. National Pharmacy Clinical Trials Advisory Group (endorsed by Royal Pharmaceutical Society) Version 1 October 2013 http://www.rpharms.com/support-pdfs/professional-guidance--n-pharmacy-services-for-clinical-trials- (accessed 21/9/15) 141013.pdf.

2. Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm (accessed 21/9/15).

3. Principles and detailed guidelines for good clinical practice as regards IMPs for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. European Commission Directive on Good Clinical Practice 2005/28/EC. April 2005.

4. Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928) implementing Commission Directive 2005/28/EC http://www.opsi.gov.uk/si/si2006/20061928.htm.

5. Annex 13 Manufacture of IMPs. Eudralex Volume 4. Good Manufacturing Practices July 2003 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf (accessed 21/9/15).