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Appendix 3: Sponsor Lead Pharmacist Role Guideline

Introduction

Based on the Royal Pharmaceutical Society (RPS) Professional Guidance on Pharmacy Services for Clinical Trials Version 1, October 2013:

The role of the pharmacist in relation to clinical research is:

a) To safeguard subjects, health care professionals and the Healthcare Provider Organisation (HPO) by ensuring that IMPs are appropriate for use and are procured, handled, stored and used safely and correctly.
b) To ensure that IMPs are managed and dispensed to patients in accordance with the duly approved current protocol.
c) To ensure that all pharmacy clinical trials procedures comply with relevant guidelines and regulations.

All pharmacy related activities, including Sponsor, and host pharmacy/pharmacist activities will usually be listed in the Pharmacy Delegation of Duties. This will be agreed with the Sponsor (but can vary depending on the specific requirements of a CTIMP) as seen in Appendix 2. The CI will be responsible for costing, securing funding and, where necessary, the agreed identification of the Sponsor Lead Pharmacist.

In the paragraphs below some of these activities are explained in more detail for guidance, these might vary according to the requirements of individual trials.

1. **Lead Pharmacist Vendor Assessment**

The Sponsor has the duty for ensuring responsibilities relating to IMP activities are delegated to individuals who are appropriately trained and qualified. This will be assessed in the Lead Pharmacist Vendor Assessment checklist. This will be performed by the Sponsor Lead Pharmacist. When noncompliance is identified, a corrective action and preventative action (CAPA) plan will be agreed with the Sponsor and implemented prior the activities involved taking place.

2. **Funding Application**

When possible the Sponsor Lead Pharmacist should be involved in the funding application to make sure all IMP management activities are adequately costed. Activities related to manufacturing and distribution, host pharmacy set up, close out and IMP management of the trial should be included.

Excess treatment costs and access to the IMP at the end of the trial will have to be evaluated at this stage.

3. **Protocol Review (IB or SmPC)**

The Sponsor Lead pharmacist must review the IMP related sections of the protocol, for safety and integrity of the research purpose, this should be done by cross-checking with the safety reference document available (IB or SmPC) and the investigational medicinal product dossier when available. Protocol sections related to IMP management include but are not restricted to: inclusion/exclusion criteria, IMP section, concomitant medication, side effects, pharmacovigilance, blinding procedure, IMP supplies, and IMP related quality management

4. **IMP Risk Assessment**

The Sponsor Lead Pharmacist should complete an IMP risk assessment (see Appendix A): This IMP risk assessment will feed back into the general risk assessment performed by the sponsor and in turn, to the monitoring plan when appropriate.

When more than one IMP is studied a separate IMP risk assessment can be used for each product.

This IMP risk assessment should be amended if a substantial amendment is approved that has the potential to change the previously identified risks.

5. **Patient Information Sheet (PIS)**

Prior to the submission of the ethics application, the Sponsor Lead Pharmacist should review the PIS for accuracy of the information provided to the participants. IMP, treatment, concomitant medications, SE and post-trial IMP access should be reviewed, cross checking with the protocol.

6. **Clinical Trials Application**

The Sponsor Lead Pharmacist should check or help when required with the provision of the IMP section of the clinical trials application including related documents ie. IB, IMPD, sIMPD, etc.

7. **Pharmacy Manual**

A pharmacy manual is required for multicentre trials. For single centre trials, a pharmacy manual will be written at the Sponsor Lead Pharmacist's discretion.

The Sponsor Lead Pharmacist should design, create or review the pharmacy manual when required. The IMP management and governance information contained must be in line with the protocol, safety reference, GMP, GDP and GCP.

As a minimum the pharmacy manual should contain information regarding:

- IMP information
- Supplies
- Storage
- Randomisation
- Blinding and unblinding procedure
- Prescribing
- Labelling and Dispensing
- Administration and precautions
- Temperature excursions
- Accountability
- IMP complaints
- IMP destruction
- Drug recall
- NIMPs
- Monitoring
- Archiving

8. IMP Supplies:

a. **Vendor Assessment:** IMP manufacturing, labelling and distribution. A vendor assessment should be done to the IMP manufacturing and distributing sites following The University of Manchester vendor assessment SOP 21, when a full audit is required the sponsor supplies vendor assessment should be used.
b. **Technical Agreement/Quality Agreement:** A technical agreement/Quality agreement must be put in place between the sponsor and the vendor to document respective responsibilities, and must include the quality standards that will be adhered to (e.g. GMP, GDP). In some cases this may be also present as a separate section in the general contract agreement with the sponsor.
The Sponsor Lead Pharmacist, must check the technical agreement(s) in place for the IMP supplies; this includes manufacturing and distribution of IMP. This should be done in accordance to Good Manufacturing Practice. The checklist detailed in Appendix B should be completed to assure the content covers all the points highlighted when relevant to the trial.

9. Conduct of the trial

Host pharmacies: For multicentre trials the Sponsor Lead Pharmacist will review the feasibility form sent to the host pharmacies, see Appendix C for guideline of questions relevant to IMP management for the feasibility form. When relevant, the Trial Lead Pharmacist should request and review the following SOPs from the local site pharmacies:

- Temperature monitoring system, out of hours procedures for temperature deviations, annual calibration certificates.
- Blinding and unblinding procedures, out of hour procedures when applicable.
- Recall SOP
- Destruction SOP or waste policy for the site.

When inadequacies, that might put at risk the safety of the participants or the validity of the research, are encountered, the sponsor should be informed and an action plan should be put in place- with the sponsor and completed by the host site prior to giving green light to the site.

10. Monitoring and auditing host pharmacies

The Sponsor will agree with the research team or CTU, when relevant, the level of monitoring required for the trial, this will include IMP management activities, and this will be reflected in the monitoring plan. The general risk assessment and IMP risk assessment will inform the monitoring plan.

11. Documentation

The Trial Lead Pharmacist will be advised to keep all correspondence and documentation related to the trial to be collated to the TMF at the end of the trial.

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Appendix A: The University of Manchester IMP Risk Assessment Form (RAF) for XXX (name of trial)

Note Appendix A is a guideline, the list of risk contained in this form is not exhaustive, this can be modified depending of the specific risks of each trial and medicinal product being investigated in the study

The RAF should be reviewed, and amended if necessary, whenever substantial amendments are made to the protocol or other key trial documentation with potential impact on efficacy or safety to the participant or the outcomes of the research.

Study Title (in full):		
Version		
IMP		
IMP class and mode of action		
Date of Completion		
Completed by		

Review and Revision record

RAF review date	Reason for review	Version of RAF reviewed	Protocol version & date	Outcome of review (revision required /no revision required)	Summary of revisions
	change requested by REC; substantial amendment (amendment number); etc.				

Where risks associated with the IMP/intervention are somewhat or markedly higher than the risk of standard care (i.e. Type B or C trials) details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described below.

Measures and controls where the risk of the intervention is considered to be comparable to standard care (i.e. Type A) need not be spelled out in detail. However basic assumptions about routine monitoring and consideration should be summarised as part of the justification provided.

IMP/Intervention	Body system	Potential Toxicities	Mitigation strategies described in the protocol
Outline any other processes that have been put in place to mitigate risks to participant safety			

	RISK/HAZARD	Is there a particular risk? Considerations/Concerns Identified Provide details of trial-specific considerations/risk concerns	Mitigation Strategies / Adaptations to minimise the hazard: Address all concerns identified Provide details of any risk-adaptations to conventional GCP management **strategies employed**	Additional monitoring methods required: discuss impact on trial monitoring requirements
1	**SAFETY**			
1.1	Complex dose schedule/ administration regime. Potential risk for dosing errors			
1.2	Dose, contra-indications/cautions in SmPC or IB correlate to protocol (e.g. inclusion/exclusion/ withdrawal criteria)			
1.3	Known/anticipated side effects addressed within the protocol			
1.4	May concomitant medications increase the risk? Are drug-drug or drug- food interactions detailed in protocol and PIS?			
1.5	Use of IMP in renal and liver impairment detailed in protocol?			
1.6	Is patient monitoring required during IMP administration?			
1.7	Is patient monitoring required after IMP treatment? Is additional safety monitoring required?			
1.8	Is process for dose escalation, dose reduction, and cessation of IMP detailed in protocol?			
1.9	Does length of treatment with IMP in trial exceed that for current clinical practice?			
1.1.0	Is an Investigator Brochure required? Is this the current version?			
1.11	Is IMP subject to any safety alerts or require any special measures?			
1.12	Have MHRA drug analysis prints (DAPs) for IMP been reviewed by the research team/CI?			
1.13	Is the CI and the research team experienced with IMP?			
1.14	Has the safety data sheet been reviewed and COSHH concerns addressed?			

1.15	Is the Sponsor producing blinding sequence? If not who is? Is this a validated system?			
1.16	Is system for allocation of blinded medication secure and fit for purpose			
1.17	Is unblinding procedure detailed in protocol? And cover 24h			
1.18	Are pharmacovigilance systems/procedures detailed in protocol e.g requirements for SAE and SUSAR recording			
1.19	Are NIMPs/rescue medicines/ challenge agents named in protocol licensed for the indication used?			
1.2.0	Is rescue medication available in treatment area and/or to take home			
1.21	Will there be an independent data monitoring committee?			
1.22	Will an annual report be submitted to MHRA?			
2	**IMP MANAGEMENT:**			
2.1	Is the supply of IMP from the drug company secure? Is there a contract +/- SLA in place?			
2.2	Is there a contract in place for clinical trial packaging and labelling activity?			
2.3	Has the manufacturer and clinical trial packaging and labelling facility been audited by UoM?			
2.4	Will IMP be stored on securely and temperature monitored on-site?			
2.5	What are storage instructions for IMP? How will the temperature be controlled and monitored during shipping, storage on site, during transport with patient and during storage in the patient's home?			
2.6	Do labels need to include BNF additional labelling requirements?			

2.7	Will additional labelling be required by site? If dosing instructions are not on the IMP label, where is documented held by patient sufficient?			
2.8	Is procedure for returned and unused IMP detailed in protocol?			
2.9	Are compliance calculations required? Whose responsibility is this?			
2.1.0	Who has responsibility for drug accountability? Does this include shipment receipt, individual dispensing and returns?			
2.11	What is procedure for destruction of returned/expired/unused IMP?			
2.12	Trial oversight. Is frequency for audit of IMP accountability and management set and appropriate?			
2.13	Is the IMP manufactured and imported from a 3rd country- QP declaration. Detail Importing company, do they have a MIA-IMP for importation			
3	**OTHER**			
3.1	Are there any additional treatment costs for drugs?			
3.2	Has continuation of IMP post end of study been considered and clearly communicated to patients?			
3.3	Is it clear to patients that the IMP contains gelatin of animal origin?			

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Appendix B: CHECKLIST and RESPONSIBILITIES FOR TECHNICAL AGREEMENTS

Tick who is responsible (UoM as Sponsor or IMP manufacturer/distributer as contractor):

Item/Activity	Sponsor	Contractor	Date	Comments
General Arrangements for Manufacturing				
Protocol provision				
If IMP manufacture takes place overseas, do they have an EU site to QP certify?				
Manufacturing License for Clinical Trials (MIA)				
QP in the MIA License for the services provided for the specific trial				
Report and advise on results of audits and inspections				
Operations in accordance with GMP (Annex 13)				
Setting up of Product Specification File. Containing all approved documents.				Containing all documentation pertaining to the manufacture, assembly and distribution of the IMP/Placebo for approval by the contract giver.
Approval of SOP and batch manufacturing records.				
Ordering process agreed				Including lead-time from order to deliver
Confidentiality arrangements				
Starting Materials for Manufacturing				
Details of starting materials agreed and filed in the PSF				Drug, excipients and packaging components
Copy of the PSF signed by both parties as part as technical agreement				
Freedom from TSE statement for any liable materials used in manufacture or packaging				
Manufacture of Active and Placebo Products				
Agreement formulation and physical parameters for any placebo product				
Agreement the analytical testing of products to be undertaken				Microbiological testing will form part of the normal release criteria (agreed protocols will be filed in the PSF).
Packaging				
Provision of details of packaging				Size, labelling instructions batch size and patient information leaflets.
Approval of Label				Signed copy filled in SPF
Details of Blinding and Randomisation				
Agreement on the control, security and disclosure arrangements for the blinding and randomisation details				
Quality Control				
Sampling and quality control inspection				Establish extra number required
Generating quality specifications for all raw materials and finished product				
Storage conditions and deviation reporting				Establish time-frame to report
Unplanned deviations reporting and action plan				
Details of analytical testing agreed with QP				
Retained Samples				
Retain samples of final product for agreed period				
Product Release and QP certification				
QP approval that the product has been manufactured/assembled in compliance with GMP and the PSF				
The QP will provide a signed certificate of conformity with each batch of product				
Transport of Product				
The product will be shipped under cold chain or ambient				

temperature as specified in the PSF				
Supply of Finished Product				
The product will be supply as directed in writing				When the process is complete and QP approval has been issued
Disposal of Surplus or Reject Product				
Disposal of any reject materials				
Complaints and Defect Reports				
Complaints will be investigated within a reasonable time scale upon written request and a written report will be provided				In case of a potentially serious complaint the initial response will be within 24h
Any quality defect in the product will be reported at any time				
Pharmacovigilance				
Advise of any suspected adverse events reported at any time				
Product Recall				
Responsibility for initiating a product recall				Information and assistance
Archiving				
Agreement on end-of-trial document archiving arrangements				
Supply of Product for Compassionate Use				
Assurance that the product will be available for compassionate use, if necessary				
Financial service provided agreed with company				
Agreement in place prior CTIMP commencing				

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Appendix C. Pharmacy Site Feasibility Form

Site Name:
Protocol:

The purpose of this document is to collect essential information on your site IMP management procedures. The information reported will be provided to The University of Manchester prior to* the *site activation visit.

STUDY LOGISTICS (To be completed by the Trial Manager)

Specify if IMP is Blinded: Yes/No
Randomisation and Product allocation system:
Initial IMP is supplied at: Local Site Activation/ Randomisation of first participant
Is IMP automatically supplied or do the site manage further supplies?:
Study Equipment is Supplied:
Estimated Pre activation visit date:
Other Important Information Site to be aware of:

IMPs	Formulation	Acceptable Temperate Range
Key Pharmacy Contacts		
Pharmacist Name:	Pharmacy Technician Name	
Email:	Email:	
Please specify Pharmacy Team's availability for	Specif	Date(s):

Item	Pharmacy Team's Processes & Procedures	Checked by Trial Manager/CTU/ Sponsor [Date & Initials]
1.	**Please provide a contact name & address for IMP deliveries**	
Pharmacy Response		
2.	**Who will check if stock is received in the correct conditions & is suitable for use?**	
Pharmacy Response		
3.	**Will IMP be stored outside of the pharmacy unit (eg satellite sites, on ward, private dialysis unit, pharmacy stores)?**	
Pharmacy Response		
4.	**Will the IMP require any significant transportation that could put the IMP at risk of a temperature excursion?**	
Pharmacy Response		
5.	**Please describe the method used (manual / electronic) to monitor IMP temperature whilst in storage & how temperature excursions are identified?**	
Pharmacy Response		
6.	**If manual temperature monitoring is used how frequently is this checked and how is this managed during weekends?**	
Pharmacy Response		
7.	**ALL temperature excursions outside of the acceptable temperature range (see study logistics above) to be reported to the trial manager/CTU. Who will be responsible for notifying the trial manager/CTU?**	
Pharmacy Response		
8.	**What procedures are in place to ensure the calibration and maintenance of the pharmacy equipment (refrigerator, thermometer & alarm) are performed according to the manufacturing guidelines?**	
Pharmacy Response		
9.	**What procedures are in place within pharmacy in the event of a power failure?**	
Pharmacy Response		
10.	**Is there a back-up refrigerator/freezer in case of an emergency? Where are they located?**	
Pharmacy Response		
11.	**How will IMP treatment requests be provided to the person dispensing the drug for each patient? (E.g how will they know which batch No. or Med No. to dispense?)**	
Pharmacy Response		
12.	**If dose is based on weight, is there a robust process in place for updating weight in the prescribing system?**	
Pharmacy Response		
13.	**Will authorised prescriptions be filed in pharmacy for review by the monitor/trial manager/CTU?**	
Pharmacy Response		
14.	**How will you ensure IMP remains within the correct storage conditions from dispensing to administration? (E.g. will reconstituted medication have an expiration date/time?)**	
Pharmacy Response		
15.	**If aseptic units are being used, when is the next shut-down for routine deep cleaning and how long does the shutdown take? Do you foresee any impact this will have on the conduct of this study?**	
Pharmacy Response		
16.	**What procedures are in place to arrange for unused/used/expired / damaged IMP to be destroyed on site or off site? Please attach SOPs**	
Pharmacy Response		
17.	**Do you prefer to use your own drug accountability log or the Sponsor's Accountability Logs? If you intend to use your own, please provide a copy for review.**	
Pharmacy Response		
18.	**What procedures are in place to ensure new pharmacy staff receives appropriate training for their role and how to manage the IMP for the study?**	

Pharmacy Response		
19.	**Will pharmacy produce study specific documents / work instructions? If yes, please list documents below as the monitor will need to review them.**	
Pharmacy Response		
20.	**Please provide the email address for IMP Notifications for your pharmacy team**	
Pharmacy Response		
21.	**Please specify if your pharmacy has any internal requirements to be in place before a Pre Activation visit date can be confirmed?**	
Pharmacy Response		
22	**Please provide any additional information including relevant SOPs ie. Recall SOP, electronic prescribing CT SOP if used**	
Pharmacy Response		
23	**Please provide CV and GCP for all members of the trials pharmacy team**	
Pharmacy Response		

Site Pharmacy Staff to complete

Completed by:_____ ***Date: _____***

Print Name:_____

Job Title: _____

Please return completed copy to the Study Manager for review