Pharmacy Manual Checklist for Clinical Trials of Advanced Therapy Investigational Medicinal Products

Pan UK Pharmacy Working Group for ATMPs

March 2023

Authors

Dr. Beatriz Duran
Consultant Pharmacist - CT & ATMPs
Manchester University NHS Foundation Trust

Amisha Desai
Advanced Clinical Pharmacist - Trials (QE)
University Hospitals Birmingham NHS Foundation Trust

Edited by:

Anne Black
Regional QA Specialist
SPS

The first stop for professional medicines advice

The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert and informed body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies.

The Pan UK PWG for Advanced Therapy Medicinal Products (ATMPs) has a clinical trials subgroup (PWG-CT), consisting of pharmacists from across the UK that specialise in Clinical trials. The aim of the group is to identify and resolve any pharmaceutical issues related to clinical trials of ATIMPs, to support the expansion of clinical trials of ATIMPs delivered within the UK and increase patient access to these novel treatments.

The Pan UK PWG-CT subgroup identified the need for standardisation and advice to sponsors regarding creation and content of pharmacy manuals for ATIMPs.

This guidance has been ratified by the National Pharmacy Clinical Trials Advisory Group.

The lead authors would like to thank all who have contributed to the production of this guidance, including Clinical Trials subgroup members of the Pan UK PWG for ATMPs.

Please contact the lead authors of this document with any questions:

Amisha Desai – Advanced Clinical Pharmacist – Clinical Trials, University Hospitals of Birmingham NHS Foundation Trust
Email: Amisha.Desai@uhb.nhs.uk

Beatriz Duran – Consultant Pharmacist – Clinical Trials and ATMPs – Manchester University NHS Foundation Trust
Email: Beatriz.Duran@mft.nhs.uk

For information about the Pan UK PWG for ATMPs, please contact:
Anne.black7@nhs.net

Introduction

This document provides a pharmacy manual checklist for sponsors to use when setting up their trial, and acts as a reference for trial sites. It will standardise, streamline and optimise the content of the pharmacy manual and reduce the number of queries to sponsors regarding the management of ATIMPs within the NHS. This will, in turn, reduce ATMP CT set up times across the UK.

The recommended content of a pharmacy manual for clinical trials of ATIMPs is given below. This list is not exhaustive, and there may be specific sponsor requirements in addition, but the following points should be addressed as a minimum:

Pharmacy Manual Checklist for Clinical Trials (CT) of Advanced Therapy Investigational Medicinal Products (ATIMP)

1. **Contact Details (sponsor, monitor, manufacturer and distribution, trial manager, etc)**

2. **Brief Summary of the Trial**

3. **Description of the ATIMP**
    - Details of the Advanced Therapy Investigational Medicinal Product (ATIMP) and any non-IMPs (NIMPs):
        - Product name
        - formulation
        - strength/concentration
        - dose
        - vial/pack size
        - primary packaging description
        - secondary packaging description including dimensions
        - ATIMP safety data sheet
    - An example of product labels should be provided, including outer shipper labels if applicable (e.g. CAR-T products). Images of the product and packaging including dimensions could be provided for this purpose.
    - Indicate whether the supply of IMP will be blinded
    - Indicate if the product is autologous or allogeneic where relevant
    - Description of genetic modification, if applicable
        - Safety data sheet
        - Requirements for handling of modified product
        - For GMO: class of the product supplied and containment level
        - Sponsor Risk assessment if required[1]
        - Information to support GMSC assessment

[1] This document may be included as an Appendix to the Pharmacy Manual

4. Randomisation

- Description of randomisation process where applicable
- Examples of documentation should be provided

5. Prescribing requirements

- Template for a prescription showing the minimum required content[2]. It is usual for sites to develop their own prescriptions in accordance with their internal procedures (e.g. electronic prescribing systems or paper based)
    - Dose to be prescribed including associated fluid volumes and infusion rates
    - If dose is weight based, details of timing and/or frequency of measurement
    - Any permitted dose banding arrangements
- Patient assessment pathway
- Concomitant medication including NIMPs, pre-medication and rescue medication, prohibited medication, cautions, etc. including dose regimens
- BSA requirements when applicable, including dose caps, calculation method
- Rounding up/down rules
- Days / weeks required for prescription prior to administration
- Dose modifications when permitted including concomitant medication
- Reporting structure to study sponsor in case of deviation

6. Blinded studies

- Blinding procedure
- Description of unblinding procedure and responsibilities within departments in hospital and Sponsor (including out-of-hours arrangements).
- Online management system (e.g. IWRS) instructions where applicable
- Example of unblinding procedures and forms[2]

7. Traceability and chain of custody requirements

- Example of chain of custody form or procedure[2]
- Example of traceability form[2]
- Example of accountability logs in pharmacy[2]
- Destruction/disposal procedure: Example of forms for destruction of unused product / containers as required[2]
- Deviation reporting system

8. Shipping and Ordering

8.1. Shipping Details

- Details of the supply chain
    - manufacturer
    - distributor(s)
    - importer (where required)

[2] This document may be included as an Appendix to the Pharmacy Manual

    - storage and
    - onward distribution partners
- List of contents expected in each shipment
    - ATIMP
    - packing list
    - shipment documents
    - QP Certification
    - Certificate of Importation / QP Oversight confirmation
    - temperature monitoring device
    - instructions for use of temperature monitoring device
- Shipping conditions

8.2. Ordering Details

8.2.1. IMP

- Details for the arrangements for ordering stock to site
    - Initial order (e.g. automatically triggered by online system / manual ordering by site or Sponsor)
    - Resupply orders (e.g. automatically triggered by online system / manual ordering by site / Sponsor).
    - Details of online ordering systems
        - System access
        - Manual or emergency orders
        - NIMP, excipient or consumable orders
    - Turnaround time for orders
    - Example of an order form when required[3]

8.2.2. Ancillary Supplies

- Description of any specific ancillary items required for preparation and administration of the dose
- Description of any ancillary supplies (e.g. syringes, needles, adaptors) to be supplied by the site:
    - Any compatibility issues
    - Process to be followed to approve local ancillary items
    - Ancillary Supply Memo (in appendix)
- Descriptions of any ancillary supplies (e.g. syringes, adaptors) provided by the sponsor including the CE marked status of each product classed as medical device
- Descriptions of any equipment provided by the sponsor and details of maintenance responsibility
- Where applicable, instructions for placing ancillary supplies orders
- Instructions for accountability of ancillary supplies. Note. New equipment may require validation

9. Receipt and Storage.

9.1. Receipt of Shipments

- Parameters for successful shipping
- Details of receipt checks to be performed (and who has responsibility for these) for each delivery:
    - shipping temperature conditions

[3] This document may be included as an Appendix to the Pharmacy Manual

    - integrity of consignment
    - what to do in the event an issue is identified during these checks
- Temperature storage requirements at facility
    - storage in shipping container
    - ultra low temperature freezer
    - vapour phase liquid nitrogen (cryopreserved products)
    - standard pharmaceutical freezer
    - standard pharmaceutical fridge
    - ambient storage
- Monitoring requirements and management of deviations.
- Details of how to identify whether the IMP has been tampered with (e.g. tamper evident seals, coded tags).
- Details of temperature monitoring device and instructions for use (or reference that it will be provided with each shipment).
- Instructions for handling of transit temperature excursions, including quarantine requirements.
- Time limits between receipt of product and preparation or administration.
- Personnel involved in product receipt.
- Procedures for:
    - Check in of product
    - Completion of which accountability logs
    - Return of shipper, if applicable or confirmation to dispose
    - PPE requirements when handling the ATIMP
- Reporting structure to study sponsor

9.2. Storage requirements

- Location of product storage at site
    - Within pharmacy
    - Within Stem Cell Lab
    - Externally contracted storage site
    - Clinical area
- Details of the storage conditions for the IMP supplied including shelf life, both as supplied and when reconstituted (i.e. prepared or thawed) where applicable.
    - storage in shipping container
    - ultra low temperature freezer
    - vapour phase liquid nitrogen (cryopreserved products)
    - standard pharmaceutical freezer
    - standard pharmaceutical fridge
    - ambient storage
- Detailed requirements for transfer of product into local controlled conditions (e.g. vapour phase liquid nitrogen tank) if applicable
- Segregation requirements during storage where applicable
- Storage and transportation requirements for returns

9.3. Monitoring of storage conditions

- Minimum requirements in terms of monitoring devices, monitoring frequency and documentation.
- Where applicable, differentiate allowable versus reportable temperature excursions.
- Where applicable, provide detailed instructions for internal transfer of IMP between storage areas and specify minimum requirements in terms of transport method, packaging, temperature monitoring logs
- Calibration requirements for monitoring devices

10. Dispensing

- Dispensing procedures (where a preparation step is involved, see section 11)
- Dispensing procedure may include where relevant:
- Labelling of product (e.g. additional considerations where product is cryopreserved)
    - Minimum label requirements (annex 13 compliance)
    - Retrieval of product from shipping unit, fridge or freezer.
    - Retrieval of product from secondary container or cassette
    - Transfer instructions of product within pharmacy or to clinical treatment area
    - Thawing / warming procedures of product as required
    - Description of thawing unit with pictures where applicable
    - PPE requirements
- Shelf life of product once thawed (where applicable)
- Procedures in case of deviations
- Documentation required
- Spillage kit requirements

11. Preparation of IMP (if applicable)

- Preparation location
    - Aseptic pharmacy
    - Pharmacy
    - Stem cell lab
    - Outsourced to alternative provider
    - Clinical area
- Provision of example Dose calculation worksheet[4]
- Provision of example Dose Preparation Worksheet[4]
- Retrieval of product from storage procedure, including thawing time (where applicable).
- Pre-requisites prior to preparation (e.g. clinical assessment of patient, clinical verification of prescription).
- Detailed instructions for the preparation of the product
- Clear step by step instructions including images
    - Specific handling requirements
    - Specific equipment and consumable requirements
    - In use shelf life of the prepared ATIMP
    - Primary packaging requirements
    - Placebo preparation instructions (where applicable)
    - Transportation of prepared product (see section 10)
    - Training material for staff involved in preparation and release

[4] This document may be included as an Appendix to the Pharmacy Manual

  - Containment and PPE requirements
  - Any specific requirements for at-risk staff (pregnant, immunocompromised etc.)
- Requirements for locally applied labels following any preparation for administration.

NOTE: Good practice guidance for the NHS requires an Annex 13 compliant label to be added to the product prior to issue. There are various regulatory requirements depending on where preparation occurs, see Outsourcing of Storage or Preparation of ATIMPs Across Legal Boundaries.

12. Administration

- Arrangements for communication between clinical unit and Sponsor for product related incidents at time of administration e.g. leaking containers, precipitation, atypical appearance etc.
- Any specific requirements for administration of the ATIMP e.g. the use of specific consumables required for administration in order to ensure compatibility with the ATIMP.
- Administration procedure.
- Guidance on viral shedding following administration where applicable.

13. Returns and disposal/waste management

- Instructions for part-used or unused ATIMP for return, including accountability and disposal/destruction instructions
- Examples of forms to use for returns and disposal/destruction- This document could be an appendix to the pharmacy manual
- Description of return of shipping containers to courier
- End of study drug reconciliation forms and communication as required

14. Complaints and Deviations

- The Sponsors complaint procedure– his document could be an appendix to the pharmacy manual
- Details of the reporting process including contact details, forms to be completed and response timeline for complaints from Site to Sponsor.
- Deviation management- when and how deviations from the established processes must be communicated to Sponsor, and how these should be documented at the site (ordinarily via the sites established deviation procedure).

15. ATIMP Recall

- Instructions for handling recalls of IMP including contact details, forms to be completed and response timeline.

16. Document Templates

- Master copies of logs and forms to be used should be included.
- Examples of forms usually required are:
  - Administration Worksheets
  - Temperature Log
  - Temperature Excursion Notification Form
  - Master Investigational Medicinal Product Accountability Log
  - Subject Specific Investigational Medicinal Product Accountability Log

Where Sponsor allows sites to use their established systems and templates in place of Sponsor provided documents, a statement to this effect should be included.

17. Out of Specification procedure

- In exceptional circumstances, Cell or Tissue-based ATIMPs may be requested for administration to patients when they do not meet their registered specification and this is in the best interests of the patient. In this case QP certification of the ATIMP cannot occur, but the product may be released with QP verification confirming GMP compliance.
- For cell or tissue-based ATIMPs, actions required by Sponsor and Site in the event of an OoS ATIMP should be described, and comply with the requirements of published guidance.

NHS Specialist Pharmacy Service

www.sps.nhs.uk