The Christie NHS
NHS Foundation Trust

5.65 Pharmacy/Pathology Management of Cellular Therapy Products (CTPs) as Advanced Therapy Medicinal Products (ATMPs)

Purpose:
To describe the procedure for managing CTPs used as ATMP which are manufactured outside The Christie NHS Foundation Trust, received, stored and issued by The Stem Cell Laboratory at The Christie Pathology Partnership which has been prescribed by an appropriate prescriber.

Policy Application:
Pharmacy Department and The Christie Pathology Partnership - Stem Cell Team

Responsibilities for implementation:
Pharmacy Department and Stem Cell Pathology Team

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Author:
Alkesh Patel (Lead Clinical Trials Pharmacist)

Authorisation:

Authorised by (Name and title)	Date Authorised
Adrian Bloor	
Robert Duncombe	
Diane Sweeney	

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Version	Date	Author	Reviewer	Comments
1.0		Nisa Khan		
2.0	2/09/20	Alkesh Patel	Diane Sweeney	

References (if applicable):
Foundation for the Accreditation of Cellular Therapy (FACT) Joint Accreditation Committee ISCT and EBMT (JACIE).*International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* 7th Edition. Nebraska Medical Centre: United States of America

HTA guide to Quality and Safety Assurance for Human Tissue and Cells for Patient Treatment v2 April 2018

Medicines and Healthcare products Regulatory Agency (MHRA). (2012) *Good Clinical Practice Guide.* London: The Stationery Office.

Number and location of any copies:
The Pharmacy Department
Q-Pulse
Stem Cell Lab SOP file

Definitions:
Advanced Therapy Medicinal Product (ATMP): A medicine for human use that is based on genes, cells or tissue engineering.

Advanced Therapy Investigational Medicinal Product (ATIMP): an ATMP as defined in Article 2(1) of Regulation 1394/2007 which is tested or used in a clinical trial (in accordance with Article 2(d) of Directive 2001/20/EC).

Cellular therapy: The administration of products with the intent of providing effector cells in the treatment of disease or support of other therapy.

Cellular therapy product (CTP): Somatic cell-based product (e.g., mobilized HPC, mononuclear cells, cord blood cells, mesenchymal stromal cells, T cells, natural killer cells) that is procured from a donor and intended for processing and administration.

Cytokine release syndrome (CRS): A non-antigen-specific toxicity that occurs as a result of high-level immune activation.

Designated Individual (DI): Individuals under whose supervision the Human Tissue Act licensed activity is authorised to be carried. They also implement the requirements of the Human Tissue Act.

Donor: A person who is the source of cells or tissue for a cellular therapy product.

DTC: Drugs and Therapeutics Committee

Immune Effector Cell (IEC): A cell that has differentiated into a form capable of modulating or effecting a specific immune response.

Storage: Holding a cellular therapy product for future processing, distribution, or administration.

Traceability: The ability to track any product through all stages of collection, processing, and Administration.

Scope
This procedure outlines the arrangements agreed by the Pharmacy Department and the Christie Pathology Partnership for storage of ATMPs which are prescribed for use in a named patient. For the purpose of this SOP, ATMP will only include CTPs. Other products within the ATMP definition are beyond the scope of this SOP.

Background

ATMPs are medicines as defined within Regulation (EC) No 1394/2007 amending Directive 2001/83/EC. The Chief Pharmacist is responsible for their use with the same responsibility as all other medicines used in the

Trust.

Cells procured from a donor and manufactured externally are classed as tissues and cells for human application until made available by the Laboratory as starting material for a medicinal product and become an ATMP at the point of manipulation of the cells. The ATMPs are stored in a designated Nitrogen vapour Dewar tank within the Stem Cell Laboratory.

It is the responsibility of the Pharmacy Department to ensure the Stem Cell Laboratory has adequate systems for traceability, release of the ATMP under a HTA Designated Individual and quality management systems which enable reporting of non-conformance.

The chain of custody for ATMPs (Appendix A) must be clear and this will be audited by Pharmacy on a quarterly and annual basis for robust oversight of these products.

Pharmacy oversight of ATMP Storage

The HTA Designated Individual for Tissues and Cells for Human Use and the appropriate designated Pharmacy individual will meet on a quarterly basis to discuss the storage facility, the Quality Management System and processes in place for ATMPs, as well as reviewing the reports of non-conformance and or storage issues encountered.

The DI is responsible for drafting a documented titled “delineation of responsibilities”. This document lists the responsibilities for each therapy.

The purpose of the document is to define the responsibilities of each party to the agreement regarding:
- The procurement of cells for use as starting material for the manufacture of an ATMP/ATIMP.
- Export of product where applicable.
- Receipt storage and issue of ATMP/ATIMP for the purpose of an ethically approved clinical trial.

The Stem Cell Laboratory Manager will either send quarterly quality reports to the designated pharmacy individual for ATMPs or will arrange a quarterly face to face meeting. This is to provide regular oversight of storage of ATMPs. Exceptions and non-conformance will be discussed at the Quality Meeting which is attended by a pharmacist.

Any issues or concerns identified by either of the lead pharmacists will be discussed with the Chief Pharmacist and HTA DI should these be of a recurrent or serious nature.

Capability and Capacity Review – Clinical Trials

The stem cell lab will carry out a capability and capacity review for the study. Pharmacy should also carry out a capability and capacity review of the study and the ATIMP involved. Both parties are responsible for highlighting if there are any procedures that are required that are not of standard pharmacy practice or standard stem cell lab practice. Pharmacy are responsible for ensuring that the product supplied complies with the relevant medicinal clinical trial legislations that is Regulation (EC) No 1394/2007 amending Directive 2001/83/EC, The Medicines for Human Use (Clinical Trials) Regulations 2004 and EudraLex Vol 4.

For any activities listed under the HTA that are required above standard practice should be listed in the delineation of responsibilities.

At study set-up a FACT-JACIE proforma is to be developed as per The Christie Cellular Therapy and

Transplant Programme Quality Manual (SCT/QM/CLINCIAL)

For clinical trial ATIMPs the FACT-JACIE must be reviewed by the clinical trials pharmacist involved in setting up the study.

Storage of ATMPs

1. ATMPS are stored in a secure storage area located on the Trust's access/delivery road. in the vapour phase of liquid Nitrogen below -150°C, or if required by protocol, in the shipper they are received in. Each ATMP is stored in a segregated area of the dedicated ATMP tank.
2. The nitrogen tank is continually monitored for temperature and for faults and externally alarmed with an escalation process involving most of the stem cell staff via the security office. The alarm system has a web based server so graphs etc can be accessed remotely. There is also a monitoring system which records all the information collected by the storage tank controllers. (POLICY SCL/POL/CRYO: Storage Policy for Cryopreserved Cells)

Storage of ATIMPs

1. The storage of ATIMPs will be as above. The sponsor may request copies of temperature logs and these should be provided by the stem cell lab team. Any temperature excursions for ATIMPs will be managed and reported the sponsor by the stem cell lab in accordance with the sponsors directions which will be confirmed at Site Initiation Visit. Products will be quarantined as per (POLICY SCL/POL/CRYO: Storage Policy for Cryopreserved Cells).

Procedure for supply of an ATMP

1. A proforma will be written by a suitably experienced clinician, as per FACT-JACIE Standards, and prescribed on iQEMO.
2. The screening pharmacist will screen iQEMO prescription. For products requiring CDF approval the screening pharmacist must ensure that the second part of CDF application for cell infusion has been completed. The reference number should be noted on iQemo. (Only for commercial products)
3. The Stem Cell lab will issue the ATMP for the named patient against the iQqemo prescription. The Stem Cell Lab will complete the pre-release checks on iQemo and release the product to the ward/department where the cells are to be administered.
4. Designated Laboratory staff will complete appropriate documentation to record the batch number and product expiry of the issued product.
5. The product will be supplied to the ward/department where the recipient is admitted and administered in accordance with relevant procedures.
6. A suitably trained nurse will administer the ATMP against the iQemo prescription, in accordance to the directions on the prescription and document receipt and administration on the appropriate forms (See Infusion of Cellular Products SOP WRD-5).

Additional steps for supply of an ATIMP

1. A clinical trials pharmacist trained in the study will clinically screen the clinical trial prescription on iQemo. The stem cell laboratory will be able to see that the script has been screened electronically and only if screened should the drug be released. This should be screened as per pharmacy clinical trials SOP 5.7 Clinical Screening of prescriptions for Clinical Trials.
2. The clinical trial prescription copy will be stored in the study-specific folder in the Stem Cell Lab with the accountability logs.
3. The HTA DI or designee will also complete the Sponsor accountability logs which will record the ATIMP batch number and expiry.
4. The product will be supplied to the ward where the recipient is admitted at the temperature at which it

has been stored by the Laboratory.

5. A suitably trained nurse will administer the ATIMP, in accordance to the directions on the prescription and document receipt and administration on the appropriate forms (See Infusion of Cellular Products SOP WD-5). The clinical trial prescription will also be completed and stored in the Trial Master File.
6. Any deviations from this SOP will be raised as a deviation in Datix and detailed in a File note and stored on the shared pharmacy drive.

Unused ATMPs

Disposal of materials from trials must be authorised by the sponsor. Disposal of clinical material is authorised by the Laboratory Medical Director.

Appendix A: Chain of Custody for ATIMPs handled by the Stem Cell Lab

This refers to the chain of custody from the point manufacture cells are received in the lab.

Arrival of ATIMPs to
The Cellular Therapy Storage Facility

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Receipt of ATIMPs

- ATIMPs to be receipted as per POLICY SCT/SCL/POL/RRP: FOR RECEIPT AND RELEASE OF PRODUCTS
- If there are any excursions on arrival this should be reported the sponsor and the product quarantined as local process. Inform the PI and the designated pharmacist of any excursions. Excursions to be communicated to the Clinical Trials Pharmacist

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Storage of ATIMPs
Store ATIMPs according to POLICY SCL/SCT/SOP/CRYO: STORAGE POLICY FOR CYROPRESERVED CELLS.
If the ATIMP storage conditions deviate from the policy they would be discussed with the sponsor and a file note would be created to abide to the specific Trial Protocol details.

→ **Quarantined ATIMP products will be stored in a segregated rack labelled "Quarantined DO Not issue"** until a decision is made as to the final fate. Follow SOP DOC2 Management of non-conforming (inc. contaminated) cellular product

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Release of ATIMPs
ATIMPs will be released once the prescription has been screened, a JACIE-FACT proforma has been signed and received by the appropriate consultant and once a 'REQUEST FOR ISSUE OF STORED IMP, AMTP OR OTHER MEDICINAL CELLULAR PRODUCT' has been completed and received in the Laboratory.
Products are released as per POLICY SCT/SCL/POL/RRP: FOR RECEIPT AND RELEASE OF PRODUCTS

Destruction/return of ATIMP product
Destruction of ATIMPs will be authorised by the Sponsor and destroyed as per Laboratory Disposal Policy.
Disposal of ATMPS will be on the death of the patient or as authorised by the Laboratory Medical Director.
For all cells returned back to the lab a '**RETURN OF CELLS TO THE LABORATORY' FORM** is to be completed by a Nurse or Clinician.

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Transfer of ATIMPs to the ward and Administration of ATIMPs
ATIMPs are transferred to the ward
Nurses will complete the CHECKLIST FOR THE THAWING AND ADMINISTERING OF FROZEN CELLS during administration of ATIMPs and return to the Laboratory