The Newcastle upon Tyne Hospitals NHS Foundation Trust

Policy for the Use of Advanced Therapy Medicinal Products

Version No.: 1
Effective From: 22 June 2017
Expiry Date: 22 June 2020
Date Ratified: 30 May 2017
Ratified By: Medicines Management Committee

1 Introduction

An advanced therapy medicinal product (ATMP) is a biological medicinal product that can be classified as either:

- a gene therapy medicinal product
- a somatic cell therapy medicinal product
- a tissue engineered product
  or a combination of the 3

As ATMPs are medicines they must meet the definition of medicines as defined within Directive 2001/83/EC and are therefore subject to the same requirements as for other medicinal products. Within the Trust the Clinical Director of Pharmacy and Medicines Optimisation is responsible for their use.

ATMPs may be sourced from an external supplier or manufactured by the Newcastle Cellular Therapies Facility (NCTF) for use by Trust patients. The licence status of ATMPs for use in the Trust can also vary e.g. an ATMP which holds a Marketing Authorisation, an unlicensed ATMP such as a Special or prepared under a 'hospital exemption', or an ATMP to be used as an investigational medicinal product within a clinical trial.

As ATMPs are specialist medicines both Pharmacy and NCTF staff have a role in ensuring they are used appropriately within the Trust.

- The role of Pharmacy is to oversee the governance arrangements and quality assurance (QA) for these specialist medicines.
- NCTF provide expertise on ATMPs which includes safe handling.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the competent authority for all medicines including ATMPs. Their remit includes
• Clinical trial authorisation for all medicinal products, including ATIMPs
• UK manufacturers or importers of ATMPs

Where ATMPs are manufactured at the NCTF, the Human Tissue Authority (HTA) regulations apply for the consent, donation, procurement, storage and testing of tissues and cells (in addition to MHRA requirements).
2 Scope

This policy covers the governance, sourcing, manufacturing, preparation for administration and technical and regulator assessment of any ATMP for use by a patient of Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH).

It covers ATMPs which are either sourced from an external supplier or manufactured at the NCTF.

Any gene or cellular products which are not deemed to be an advanced therapy medicinal product must be managed in line with the appropriate regulations. Human Tissue Authorities (HTA) regulations and guidance and will not be considered further within this document but further information can be found at https://www.hta.gov.uk/

3 Aims

The aim of this policy is to ensure ATMPs are used and governed appropriately within NuTH.

4 Duties (Roles and responsibilities)

New Interventional Procedure Committee
Assessment and approval of somatic cell therapy and tissue engineered products and combination products (e.g. somatic cell and gene therapy product) that are to be used by NuTH patients.

Genetically Modified Organism Safety Committee
Assessment and approval of gene therapy medicinal products and combination products (e.g. somatic cell and gene therapy product) that are to be used by NuTH patients.

The pharmacy department are responsible for:
- Providing advice and oversight of MHRA Manufacturing licences
- Providing advice and oversight re preparation activities for ATMPs
- Auditing the Cellular Therapies Facility as necessary to ensure GCP compliance
- Sourcing licensed and unlicensed ATMPs from appropriate external suppliers.
- Overseeing GCP activities performed in NCTF
- Approving procedures relating to handling and storage of ATMPs

NCTF are responsible for:
- Manufacture and release of unlicensed ATMPs under the Trusts Manufacturers Specials Licence
- Manufacture of ATIMPs for use in clinical trial
- Providing training to NuTH staff as needed
- Oversight and provision of technical expertise and associated approvals as needed
- Reconstitution and storage of ATMPs which are not manufactured by NuTH.
### 5 Definitions

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced Therapy Medicinal Product (ATMP)</strong></td>
<td>A biological medicine for human use that is a gene therapy, somatic cellular therapy or tissue engineering product.</td>
</tr>
<tr>
<td><strong>Advanced Therapy Investigational Medicinal Product (ATIMP)</strong></td>
<td>An investigational medicinal product used within a clinical trial. The medicine, for human use, is a gene therapy, somatic cellular therapy or tissue engineering product.</td>
</tr>
<tr>
<td><strong>Cellular Product</strong></td>
<td>A product based on cells or tissues which have not been substantially modified and are for homologous use.</td>
</tr>
</tbody>
</table>
| **Gene Therapy Medicinal Product (GTMP)**                                 | GTMP means a biological medicinal product which has the following characteristics:  
  a) It contains an active substance which contains or consists of a recombinant nucleic acid used in, or administered to human beings, with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;  
  b) Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.  
GTMP does not include vaccines against infectious diseases.                  |
| **Somatic cell therapy medicinal product**                               | Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:  
  a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;  
  b) Is presented as having properties for, or is used in or administered to human beings, with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues. |
| **Tissue engineered product**                                             | A medicinal product that; Contains or consists of engineered cells or tissues and is administered to human beings with a view to regenerating, repairing or replacing human tissue. A tissue engineered |
product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>A medicinal product is:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• any substance or combination of substances presented as having properties of preventing or treating disease in human beings</td>
</tr>
<tr>
<td></td>
<td>• any substance or combination of substances that may be used by or administered to human beings with a view to restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action, or making a medical diagnosis</td>
</tr>
</tbody>
</table>

| Special | An unlicensed medicine manufactured or imported under a manufacturing specials (MS) licence. |

| Hospital exemption (Not widely used in the UK) | Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient. ATMPs prepared under this exemption are deemed unlicensed medicines. |

6 Policy

An overview of the policy is provided in Appendix 1. Contact details for key personnel is provided in Appendix 2.

6.1 Receipt of a Request for the use of an ATMP

The definition of an ATMP, stated within Directive 2001/83/EC, should be referred to prior to submitting the request for a new ATMP to ensure the desired product is in fact classified as an ATMP. Where there is any ambiguity the Assistant Director of Pharmacy – Quality Assurance should be contacted.

Note: Requests for manufacture of a cellular product from an external body will need to be assessed to determine if they are an ATMP (and are therefore a medicine) or they are not actually a medicine (and therefore not within the scope of this policy). The Assistant Director of Pharmacy – Quality Assurance or deputy is responsible for assessing the legal classification of the requested product.
As for all new medicines - the Access to Drugs Policy must be followed for the request a new ATMP (excluding those for use within a clinical trial) to be use within NuTH. Approvals of ATMP products will be performed by the relevant committees as described in section 6.3 below.

Where the ATMP is classified as an unlicensed medicine, the Unlicensed Medicine Policy must be followed in addition.

ATMPs which are to be used within a clinical trial must be requested following the Research and Development / Research Governance Policy.

An ATMP which is deemed an investigational medicinal product may also be referred to an as an ATIMP (Advanced therapy investigational medicinal product or a clinical trial investigational medicinal product (CTIMP).

6.2 Technical and Regulatory Assessment
A flow diagram of this process is defined in Appendix 3.

An assessment will be made by the Pharmacy Department (in liaison with the NCTF where necessary) to determine:

- If the ATMP requires to be manufactured (e.g. does it require substantial manipulation or is it for a different physiological function).
- If manufacturing authorisations / licences are needed (as appropriate) for either the manufacture or sourcing of an ATMP. See 6.4. below
- If the ATMP requires storage or preparation manipulation prior to administration.
- The location in which any additional preparation steps (if necessary) are to take place e.g. within the NCTF or within the clinical area.
- Any additional training needs re storage and handling of the ATMPs.
- The quality assurance requirements for any starting materials needed for the manufacture of an ATMP.

6.3 Approvals
All requests for new ATMPs will be subject to governance procedures within the Trust including approval by the appropriate committee, Trust policies and formulary control.

Approval Committees:
Somatic cell therapy (SCT) and tissue engineered medicinal product (TEP)
- New Intervention Procedures Committee

Gene therapy medicinal product
- Genetically Modified Organism Safety Committee

Combination products (i.e. SCT/TEP and Gene therapy product)
- New Intervention Procedures Committee and the Genetically Modified Organism Safety Committee
ATMPs for use as part of a clinical trial will be, in addition, subsequently approved as per the Research and Development / Research Governance Policy.

The Unlicensed Medicines Policy must also be followed for any ATMPs which are deemed unlicensed e.g. a ‘Special’.

6.4 Sourcing
ATMPs will either be sourced from an external provider or manufactured by the NCTF under the Trust’s MHRA manufacturer’s authorisation for IMPs or the Manufacturer’s Specials Licence.

ATMPs purchased from an external source
- Pharmacy Procurement are responsible for sourcing licensed or unlicensed ATMPs for use within the Trust. This will be in line with current policies and procedures for the general purchase of medicinal products.
- The Unlicensed Medicines Policy and associated pharmacy procedures must be followed to source an unlicensed ATMP.
- All ATMPs must be sourced from an appropriate pharmaceutical supplier who holds the necessary MHRA licence / authorisation to sell / supply medicinal products e.g. a wholesale dealer licence.
- The requestor of an ATIMP must liaise with the Pharmacy Clinical Trials team.

ATMPs requiring manufacture by NCTF
- Supplier qualification will be performed by the NCTF in line with Good manufacturing practice (GMP) requirements.

6.5 Manufacturing
The technical assessment will determine if any manufacturing activity by the NCTF is necessary.

The Newcastle Cellular Therapies Facility holds appropriate MHRA authorisations / licences (MIA (IMP) or MS) to manufacture bespoke ATIMPs for the use within clinical trials and unlicensed medicines i.e. Specials. Release of any ATMP will be performed by the appropriate personnel relevant to the manufacturing authorisation e.g. Qualified Person (QP) or Releasing Officer.

Pharmacy will provide advice and oversight of Trust Manufacturing licences and Qualified Person services.

Where unlicensed ATMPs are being sourced from an external supplier, the appropriateness of the manufacturer will be scrutinised for by the Pharmacy department (Quality Assurance) along with the pharmaceutical quality of the medicine.

6.6 Preparation and Administration
The Trust Injectable Medicines Policy and Supporting Information must be adhered to by any staff member preparing or and administering an ATMP in the clinical area.
The technical assessment performed by pharmacy will determine the location that an ATMP will be prepared i.e. NCTF or the clinical area. The technical assessment will include consideration of the ATMP shelf life and operator safety. Preparation within NCTF is the preferred location if the shelf life of the prepared ATMP allows for this.

ATMPs to be prepared for administration in the NCTF
ATMPs requiring preparation in the NCTF facility will be prepared by NCTF staff according to internal procedures and then transferred to the clinical area for administration by a trained member of clinical staff. NCTF are responsible for providing a labelled, ready to administer dose.

ATMPs to be prepared for administration in the clinical area
NCTF staff are responsible for transferring the ATMP to the clinical area and then subsequently preparing a labelled, ready to administer ATMP (this may include thawing of the product). A trained member of staff e.g. registered nurse will then administer to the patient. Alternatively the preparation can be performed by a trained member of the clinical team (e.g. a registered nurse) this training will be overseen and assessed by NCTF staff.

6.7 Receipt, Storage and Handling
Pharmacy or NCTF (following a pharmacy approved SOP) must receive all ATMPs. ATMPs often require specialist handling and storage e.g. in vapour phase liquid nitrogen dewers. This is therefore often performed by NCTF staff as they have appropriate storage facilities and expertise to do so. Where storage or handling of an ATMP is required in the clinical area / by clinical staff NCTF is responsible for providing training and advice re appropriate storage / handling. The clinical staff are responsible for monitoring any specialist storage devices within their specialist area.

Storage of an ATMP for use in a clinical trial must be stored in a pharmacy approved area. Storage within the clinical area (e.g. as emergency access is required) is subject to the outcome of a pharmacy led risk assessment to ensure appropriate controls can be implemented. Pharmacy Clinical Trials SOPs are to be followed to perform this assessment.

Pharmacy are responsible for overseeing and approving all procedures relating to the handling and storage of ATMPs.

NCTF are responsible for providing all procedures relating to handling and storage of ATMPs.

6.8 Clinical Trials
The Research and Development / Research Governance Policy must be followed for any ATMP used as an investigational medicinal product as part of a clinical trial.

Pharmacy is responsible for GCP oversight of any clinical trial in which the ATMP is manufactured at NCTF or the ATMP is administered to a NuTH patient.

NCTF is responsible for technical oversight of any clinical trial in which the ATMP is manufactured at NCTF or the ATMP is administered to a NuTH patient.
All requests / orders for ATIMPs are to be provided to pharmacy or NCTF as defined on the specific order form.

Pharmacy will audit the Cellular Therapies Facility for compliance to GCP when required.

6.9 Training
NCTF are responsible for training NuTH staff on appropriate handling and storage of ATMPs. They are also responsible for providing training on preparation of these specialist products when needed. Clinical staff are not permitted to prepare ATMPs without this additional training and competency assessment.

7 Equality and Diversity

The Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This document has been appropriately assessed.

8 Monitoring Compliance

<table>
<thead>
<tr>
<th>Standard / process / issue</th>
<th>Monitoring and audit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method</td>
</tr>
<tr>
<td>The approval, receipt and use of ATMPs</td>
<td>I Audit</td>
</tr>
</tbody>
</table>

9 Consultation and review

This Policy has been reviewed by Medicines Management.

10 Implementation (including raising awareness)

Policy content communicated to all Trust staff via a Policy Bulletin
Policy content communicated to all Pharmacy Staff via team briefings
Policy content communicated to Medical Staff via the Medicines Management Committee
Policy content communicated to Registered Nursing staff via relevant Clinical Teams
Policy content communicated to Cellular Therapies Staff via Quality Meeting
Policy content communicated to Research and Development via Pharmacy Clinical Trials

Author: Assistant Director of Pharmacy - Quality Assurance
11 References
http://ec.europa.eu/health/documents/eudralex/vol-1/ Accessed 13.06.16


12 Associated documentation

Access to Drugs Policy
Injectable Medicines Policy and Supporting Information
Medicines Policy
Research and Development / Research Governance Policy
Unlicensed Medicines Policy

Appendix 1 – Overview of Process
Appendix 2 – Technical and Regulatory Assessment
Appendix 1 – Overview of Process

Hospital receives request to use a cellular/gene product

Is it a medicine?

No

Holds a Marketing Authorisation (MA)

Yes

Unlicensed Medicine (Special or Hospital Exemption)

Advanced Therapy Investigational Medicinal Product (ATIMP)

Technical and regulatory assessment (See appendix 3)

Hospital Governance Approval required:
• New Intervention Procedures Committee AND / OR
• Genetically Modified Organism Safety Committee

Consider EU Tissue & Cells Directive (EUTCD) (HTA in UK)

Implement via SOP with Pharmacy and Cellular Therapy team approach.

Advanced Therapy Investigational Medicinal Product (ATIMP)
## Appendix 2 – Contact Details for Key Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Designation</th>
<th>Tel</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne Black</td>
<td>Assistant Director of Pharmacy – Quality Assurance Qualified Person</td>
<td>0191 2823812</td>
<td><a href="mailto:Anne.black@nuth.nhs.uk">Anne.black@nuth.nhs.uk</a></td>
</tr>
<tr>
<td>David Caulfield</td>
<td>Trust Quality Controller Qualified Person</td>
<td>0191 2820920</td>
<td><a href="mailto:David.caulfield@nuth.nhs.uk">David.caulfield@nuth.nhs.uk</a></td>
</tr>
<tr>
<td>Dean Bradley</td>
<td>Quality Manager: Newcastle Cellular Therapies Facility</td>
<td>0191 2418822</td>
<td><a href="mailto:Dean.bradley@newcastle.ac.uk">Dean.bradley@newcastle.ac.uk</a></td>
</tr>
<tr>
<td>Maria Allen</td>
<td>Pharmacy Clinical Trials Team Operations Manager</td>
<td>0191 2839321</td>
<td><a href="mailto:Maria.allen@nuth.nhs.uk">Maria.allen@nuth.nhs.uk</a></td>
</tr>
</tbody>
</table>
Appendix 3 - Technical and Regulatory Assessment

Does product require a manufacturing step? (i.e. substantial manipulation)

Yes

Manufacturers authorisation required:
• MIA (IMP) for ATIMPs.
• Manufacturer’s Specials (MS) or Hospitals Exemption (HE) for unlicensed ATMPs.

No

Are the cells being used for a different physiological function?

Yes

No

If ATIMP, have the cells been QP released into the EU?

Yes or n/a

Is a preparation step required prior to administration?

Yes

Does stability allow for aseptic unit preparation?

Yes

Prepare in dedicated aseptic unit at NCTF

No

Expert staff prepare in clinical area.

No

Pharmacy and nursing staff require training re storage and handling from Cellular Therapies staff

Yes

Issue ready to administer
The Newcastle upon Tyne Hospitals NHS Foundation Trust

Equality Analysis  Form A

This form must be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval.

PART 1

1. Assessment Date: 20 Apr. 17

2. Name of policy / strategy / service:
   Policy for the Use of Advanced Therapy Medicinal Products

3. Name and designation of Author:
   Anne Black. Assistant Director of Pharmacy - QA

4. Names & designations of those involved in the impact analysis screening process:
   Lauren Stewart. Quality Assurance Pharmacist

5. Is this a: Policy x Strategy □ Service □
   Is this: New x Revised □
   Who is affected Employees x Service Users □ Wider Community □

6. What are the main aims, objectives of the policy, strategy, or service and the intended outcomes? (These can be cut and pasted from your policy)
   To ensure the safe introduction and use of cellular and gene based medicines

7. Does this policy, strategy, or service have any equality implications? Yes □ No x

If No, state reasons and the information used to make this decision, please refer to paragraph 2.3 of the Equality Analysis Guidance before providing reasons:
   This policy states approved practice for the ordering and handling for a group of innovative medicines.
### 8. Summary of evidence related to protected characteristics

<table>
<thead>
<tr>
<th>Protected Characteristic</th>
<th>Evidence, i.e. What evidence do you have that the Trust is meeting the needs of people in various protected Groups</th>
<th>Does evidence/engagement highlight areas of direct or indirect discrimination? If yes describe steps to be taken to address (by whom, completion date and review date)</th>
<th>Does the evidence highlight any areas to advance opportunities or foster good relations. If yes what steps will be taken? (by whom, completion date and review date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race / Ethnic origin (including gypsies and travellers)</td>
<td>Patient characteristics are considered when prescribing medication.</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sex (male/ female)</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Religion and Belief</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sexual orientation including lesbian, gay and bisexual people</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Disability – learning difficulties, physical disability, sensory impairment and mental health. Consider the needs of carers in this section</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gender Re-assignment</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Marriage and Civil Partnership</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maternity / Pregnancy</td>
<td>As above</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### 9. Are there any gaps in the evidence outlined above? If ‘yes’ how will these be rectified?

No

### 10. Engagement has taken place with people who have protected characteristics and will continue through the Equality Delivery System and the Equality Diversity and Human Rights Group. Please note you may require further engagement in respect of any significant changes to policies, new developments and or changes to service delivery. In such circumstances please contact the Equality and Diversity Lead or the Involvement and Equalities Officer.

Do you require further engagement? Yes [ ] No [x]

### 11. Could the policy, strategy or service have a negative impact on human rights? (E.g. the right to respect for private and family life, the right to a fair hearing and the right to education?)

No
PART 2

Name: Anne Black

Date of completion: 20.4.17

(If any reader of this procedural document identifies a potential discriminatory impact that has not been identified, please refer to the Policy Author identified above, together with any suggestions for action required to avoid/reduce the impact.)