Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Trust Policy for GTMP/GTIMP Approval

Creator: University Hospital of Wales & University Hospitals Bristol & Weston NHS Foundation Trust
Document version number: V2.1
Date written: September 2020

End user rights:

This document is shared with permission for re-use to distribute, remix, adapt, and build upon the material in any medium or format for non-commercial purposes only, so long as the attributions listed below are given.

Attributions: University Hospital of Wales & University Hospitals Bristol & Weston NHS Foundation Trust

This document is made available under a Creative Commons Attribution - NonCommercial 4.0 International License as described here: https://creativecommons.org/licenses/by-nc/4.0/

The information, materials and any opinions contained in this document are provided for general information and educational purposes only, are not intended to constitute legal or other professional advice and should not be relied on or treated as a substitute for specific advice relevant to particular circumstances. Although we make all reasonable efforts to ensure the information is up to date, we make no representations, warranties or guarantees in that regard. In no event shall the creator(s) be liable for any direct, indirect, special, consequential or other damages that are related to the use or reliance whatsoever in the content of the document or any part thereof.

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Trust Policy for GTMP/GTIMP Approval

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

Trust Policy for GTMP/GTIMP Approval

Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

01 September 2020

Background

As Gene Therapy Medicinal Products (GTMPs) and Gene Therapy Investigational Medicinal Products (GTIMPs) are Advanced Therapy Medicinal Products (ATMPs), it is important that organisations have a defined governance process in place for their approval and implementation. This document gives an example of a Trust Policy for approval of GTMPs/GTIMPs by a Trust Genetic Modification Safety Committee (GMSC).

Trust policies for assessment and approval of GTMPs/GTIMPs and GMSC membership/terms of reference, should take account of recommendations set out in;

Pan UK Pharmacy Working Group for ATMPs. Gene Therapy Medicinal Products; Governance and Preparation Requirements. Available from
https://www.sps.nhs.uk/wp-content/uploads/2019/09/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-issue-2.pdf

National institutional readiness checklists, should also be implemented for in-vivo and ex-vivo GTMPs, to ensure that local procedures are comprehensive.

https://www.sps.nhs.uk/wp content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-ex-vivo-cell-based-Gene-Therapy-Medicinal-Products-V1-July-2020-.pdf

https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-in-vivo-virus-based-Gene-Therapy-Medicinal-Products-V1-July-2020.pdf

Consideration should also be given to the governance of non gene therapy ATMPs. Some organisations have a separate committee for these ATMPs, whilst others consider all ATMPs in their GMSC

INDUSTRIAL STRATEGY
UK Research and Innovation
Coordinated by CATAPULT Cell and Gene Therapy

Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Example Trust Policy for GTMP/GTIMP Approval

To ensure safe handling and administration of Genetically Modified Organism (GMO) *in vivo* gene therapies (Class I or II biohazards) to minimise any risk to human health and the environment.

Policy Statement

To ensure that GTMPs and GTIMPs are deployed in accordance with regulations to minimise any risk to patients, staff, other members of the public and the environment.

Objectives

- Approval for use and safe management including compliance with relevant regulations
- Appropriate Health and Safety Executive notification
- Review via risk assessment of all licensed/unlicensed GTMPs and GTMPs used in clinical trials by the GMSC
- Clarification of roles and responsibilities of those involved in the delivery of GTMPs/GTIMPs
- Provide advice on the potential risks to humans and the environment associated with the use of Genetically Modified Organisms (GMO) and how risks may be minimised.

Scope

This policy relates to the use of all GTMPs/GTIMPs on Trust premises and/or involving Trust employees. The policy considers GTMPs/GTIMPs that represent a moderate hazard (Class I & 2) to people and the environment. Class 3 & 4 GTMPs/GTIMPs are not considered within this policy.

Associated Documents:

Approved by: Genetic Modification Safety Committee	
Date:	
Review date:	

Summary of reviews/amendments			
Version Number	**Date of Review Approved**	**Date Published**	**Summary of Amendments**
	Date of Committee or Group Approval		

INDUSTRIAL STRATEGY
UK Research and Innovation
Coordinated by CATAPULT Cell and Gene Therapy

Glossary

BSO	Biological Safety Officer is a specialist adviser on matters relating to safe handling of biological materials. The BSO advises the GMSC on matters of safety and reviews recommendations and requirements from the GMSC. The BSO assists the clinical trial teams in undertaking the actions required to comply with statutory obligations.
Gene therapy medicinal product (GTMP)	A gene therapy medicinal product is defined as 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.
Gene therapy investigational medicinal product (GTIMP)	A GTMP (see above) which falls under the classification of an Investigational medicinal product (IMP) in a clinical trial.
GCP	Good Clinical Practice (GCP) is an international quality standard that is provided by International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. See also the European Commission Guidance: Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810)
GMO	Genetically modified organism. An organism (with the exception of humans) in which 'the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination' using 'recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules, produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.

GMO - IMP	Genetically modified organisms which fall under the classification of an Investigational Medicinal Product (IMP) in a clinical trial. These can be genetically modified viral vaccines and some gene therapy medicinal products including viral vectors and cells genetically modified by viral vectors.
GMM	Genetically modified microorganisms GMMs are a category of GMOs which includes bacteria, viruses, parasites and fungi.
GMSC	Genetic Modification Safety Committee, a committee that risk assesses and approves use of gene therapy medicinal products and gene therapy investigational medicinal products in the organisation.
HSE	Health and Safety Executive HSE is Great Britain's independent regulator for work-related health, safety and illness. It operates and enforces legislation that aims to control the risks to human health and the environment arising from activities involving GMOs in containment under the Genetically Modified Organisms (Contained Use) Regulations 2014.
IB	Investigator's Brochure The IB is a compilation of the clinical and non-clinical data on the IMP(s) that are relevant to the study of the product(s) in human subjects
IMP	Investigational Medicinal Product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form
IMPD	Investigational Medicinal Product Dossier The IMPD includes information related to the quality, manufacture and control of the Investigational Medicinal Product.
MHRA	The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. They regulate clinical trials of medicines and ensure compliance with statutory obligations.

PI	Principal Investigator. The PI is responsible for the conduct of a clinical trial at a trial site.
SOP	Standard Operating Procedure Detailed, written instructions to achieve uniformity of the performance of a specific function.
Sponsor	The organisation who, under the Medicines for Human Use (Clinical Trial) Regulations 2004 takes responsibility for initiating, management and financing of the Trial. Sponsors may be academic institutions or commercial companies.
The Regulations	Genetically Modified Organisms (Contained Use) Regulations (2000) as amended.

1. Introduction

As GTMPs/GTIMPs are classified as Advanced Therapy Medicinal Products (ATMPs), a defined organisational governance process is required for approval and implementation.

This policy sets out the requirements for Trust approval of these medicines, with review by the Genetic Modification Safety Committee (GMSC) of;

- Use of GTIMPs within clinical trials
- Therapeutic use of GTMPs, including off-licence use outside of clinical trials

2. Regulatory Requirements

The GMSC must ensure that GTMPs/GTIMPs are implemented in accordance with the legislation and guidance outlined in Table 1. GTIMPs and unlicensed GTMPs used outside of clinical trials are regulated by the MHRA and HSE. Licensed GTMPs are governed by the medicines regulators only. Unlicensed GTMPs used outside of clinical trials and out of specification GTMPs must also be used in accordance with the Trust Unlicensed Medicines Policy.

Table 1 GTMP legislation and guidance documentation
Human Medicines Regulations 2012 SI: 2012 - No. 1916
Regulation (EC) NO 1394/2007 On Advanced Therapy Medicinal Products ("The ATMP Regulation")
Health and Safety Executive (HSE) Genetically Modified Organisms (Contained Use) Regulations 2014
The Medicines for Human Use (Clinical Trials) Regulations 2004
If the gene therapy product is being used in a clinical trial reference should be made to the following :-
Clinical Trials Directive 2001/20/EC
Medicines for Human Use (Clinical Trials) 2004 SI: 2004- No.1031 as amended

3. Classification and Containment Levels for GTMP/GTIMP

There are four classes of activities according to the regulations. The classification is based on the level of risk to humans and the environment.

Class 1 – activity of no or negligible risk for which containment level 1 is appropriate to protect human health and the environment

Class 2 – activity of low risk for which containment level 2 is appropriate to protect human health and the environment

Class 3 – activity of moderate risk for which containment level 3 is appropriate to protect human health and the environment

Class 4 – activity of high risk for which containment level 4 is appropriate to protect human health and the environment

The classification of the activity involving the genetically modified organism (GMO) is determined by the containment and control measures identified as necessary via the risk assessment. Containment measures are detailed in Schedule 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014 available at: **http://www.hse.gov.uk/pubns/priced/l29.pdf**

Most activities involving GTMP/GTIMP that are currently in clinical trials and in development are expected to be class 1 or 2. For example:

- Containment level 1 is suitable for class 1 activities involving GTMPs such as replication incompetent adeno-associated viruses
- Containment level 2 is required for class 2 activities such as the use of conditionally replicating virus vectors.

However, the classification for each individual activity must be determined by the risk assessment process that identifies necessary control measures from Schedule 8. Control measures identified from the highest containment level determine the class of the activity. For further details on risk assessment of GMOs see the HSE Compendium of guidance Part 2: **http://www.hse.gov.uk/biosafety/GMO/acgm/acgmcomp/part2.pdf**

This Policy considers Class 1 and Class 2 activities, involving GTMP/GTIMP. Investigators wishing to undertake a clinical trial involving a Class 3 GMO must contact the GMSC Chair at the earliest opportunity to discuss the feasibility of the proposed trial. The Trust will not use Class 4 GMOs.

4. HSE notification

HSE notification is required for;

- Clinical trials using GMO containing GTIMPs
- Unlicensed GTMPs containing GMO

For further details refer to the HSE GMO (Contained Use) Regulations 2014 or the Pan UK PWG for ATMPs – Gene Therapy Governance and Preparation Requirements (available from www.sps.nhs.uk, **https://www.sps.nhs.uk/wp-content/uploads/2019/09/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-issue-2.pdf).**

- **Initial notification:** On the first occasion of using an unlicensed or clinical trial GMO, the HSE premises notification form- notification of the intention to use premises for contained use activities should be completed.
  - The GMSC chair must receive an acknowledgement of receipt of the notification from the HSE prior to any GTMP work commencing in the organisation.
  - The GMSC may deem that the first contained use does not require HSE notification via the premises notification form (eg Class 1 status only) in which case, a summary of the risk assessment should be submitted along with information on waste management and details of any expert advice received.
  - For subsequent Class 1 activities, no further permission is required after the first notification.

- **Subsequent notifications:** Prior to the commencement of any related work, the HSE must be notified of the intention to undertake activities involving Class 2 GTIMPs:
  - Activity must be notified to the HSE though submission of the 'CU2 - Notification of intention to conduct individual contained uses' form (available on the HSE website **https://www.hse.gov.uk/forms/genetic**).
  - Where notification of the premises has not occurred previously, 45 days must elapse from acknowledgement of receipt of the notification and activity commencing.
  - If premises have been previously notified, Class 2 contained work may commence upon acknowledgement of receipt.

5. Risk Assessment

- The responsible Consultant (GTMPs) or Principle Investigator (GTIMPs) will complete a GTMP/GTIMP risk assessment proforma (Appendix A), considering;
  - the type of GTMP/GTIMP, planned use and location
  - the product, patient and waste pathway (to include accidental spillage)
  - available staff expertise
  - specific medicine requirements including the Summary of Product Characteristics (SPC)

- Input will be obtained from the local BSO, ATMP and Specialist Clinical pharmacists, and other experts as necessary.
- To be approved, a Risk Assessment should demonstrate
  - that risks have been thoroughly assessed; **and**
  - measures to contain and minimise the identified risks are adequate and feasible.
- The risk assessment will identify the level of risk and hazards posed by working with the medicine. Assessors will take note of applicable guidance, policy and legislation.
- The level of risk determines the containment level required for safe handling of the GTMP. Further details on containment measures may be found in Schedule 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014 **https://www.hse.gov.uk/pubns/priced/l29.pdf.**
  - Containment Level 1 will apply to no or negligible risk work for class 1 GTMPs that are unlikely to result in harm to humans or the environment.
  - Containment Level 2 will apply to low risk work for class 2 ATMP GTMPs that are able to cause human disease.
- The risk assessment will establish if the ATMP requires special handling or special personal protective equipment or other additional containment measures to minimise risk. Specific work instructions, handling protocols and/ or SOPs covering the agreed arrangements may be issued. Measures may include documented training and competency assessments; occupational health involvement; specific additional facilities
- HSE compendium part 2 should be consulted for further details of risk assessment of GMO **https://www.hse.gov.uk/biosafety/GMO/acgm/acgmcomp/part2.pdf**

6. Further approvals required prior to implementation of marketed GTMPs

- Pharmaceutical company site approval
- JACIE accreditation/maintenance of accreditation for cellular GTMPs
- Selection as a commissioned centre

7. Duties and responsibilities

Trust Genetic Modification Safety Committee

The GMSC is a subcommittee of the Trust Medicines Management Committee.

[For suggested membership and example terms of reference, consult the Pan UK Pharmacy Working Group for ATMPs. Gene Therapy Medicinal Products; Governance and Preparation Requirements. Available from **https://www.sps.nhs.uk/wp-content/uploads/2019/09/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-issue-2.pdf]**

The GMSC will;

- Review Trust GTMP/GTIMP risk assessments and where applicable, clinical trial protocols and other relevant trial documentation.
- Notify HSE of unlicensed or clinical trial use of GMOs and ensure acknowledgement of notification is received.
- Provide the Trust and where applicable, the clinical trial sponsor with a written risk assessment of the Class of GTMP/GTIMP and its potential risks.
- Decide if proposed investigational or therapeutic use of GTMPs/GTIMPs may safely be undertaken within the Trust and communicate this decision to all relevant parties.
- Recommend specific safety measures necessary to protect patients, staff, public and the environment and ensure appropriate arrangements are detailed for receipt, storage, preparation and handling, transportation, disposal and spillage of the GTMP/GTIMP.
- The GMSC will confirm one of the following and notify the Trust Medicines Management Committee of its decision:
    - that adequate measures have been considered and/or arranged (includes handling, use and disposal of the product) for use to commence
    - that further risk reduction measures need to be put in place before use can commence
    - that use is not approved (should not take place) at the Trust

Trust Research Team will (in relation to GTIMPs only);

- Coordinate the GMSC review, notifying the Principal Investigator (PI) and/or trial sponsor of the procedure and provide the Trust GTIMP risk assessment proforma to be completed.
- Co-ordinate notification to the HSE and appropriate communication of HSE acknowledgement of notification.
- Before a clinical trial is approved, ensure that:
    - the GMSC has reviewed and approved the risk assessment and documentation has been archived by the secretary
    - Pharmacy is informed of the trial and is satisfied that appropriate arrangements (as applicable for the trial) for receipt, onsite storage, onsite preparation and handling, onsite transportation, and disposal of GTIMP, in line with GCP, will be in place prior to the commencement of the trial.

Principal Investigator (GTIMPs) or Responsible Consultant (marketed or unlicensed GTMPs) will;

- Complete the GTMP/GTIMP risk assessment proforma in consultation with the Sponsor where applicable.
- Submit the risk assessment and where appropriate the clinical trial protocol, relevant SOPs, IB and IMPD (if available) to the GMSC for review.
- Aid in preparing the notification to the HSE if required.
- Ensure that necessary SOPs reflecting the requirements of the GMSC are in place.
- Notify pharmacy as early as possible, provide associated documentation required by pharmacy and discuss to ensure compliance with Good Clinical Practice (GCP) aspects of medicines management.
- Ensure the clinical team and staff who may come into contact with the GTIMP/GTMP are appropriately trained in the receipt, onsite storage, onsite preparation and handling, onsite transportation, administration and disposal of GTMP/GTIMP in line with relevant regulations and GCP for GTIMPs. All training and demonstrated competencies should be documented. For clinical trials, this should be recorded in the site file and the individuals named on the trial delegation log.

Lead Advanced Therapy Medicinal Products Pharmacist and/or the Pharmacy Clinical Trial Lead or Lead Specialist Clinical Pharmacist will;

- Work with the PI (and others where relevant) to ensure that the on-site arrangements for receiving, handling, storage and destruction of the GTIMP will be in compliance with GCP and relevant regulations.
- Work with the Lead Clinician non-trial to ensure on-site arrangements for receiving, handling, storage and destruction the GTMP will be in compliance with regulation and good practice.
- Ensure that suitable arrangements for dispensing or preparation will be in place, if applicable at site.
- Ensure that suitable arrangements will be in place for transportation from on-site storage or on-site preparation to administration area, and that storage in the administration area, if applicable, is compliant with the relevant requirements.

Non-trial use of GTMPs

- For non-trial use, the Clinical Director of the Directorate/Division using the medicine will be responsible for all aspects of safe delivery and disposal of the GTMP following approval by the GMSC.

7. References

Department of Health. Advanced Therapy Medicinal Products Guidance: regulation and licensing. Published on-line 26 January 2015. **https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing**

Medicines and Healthcare products Regulatory Agency. Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products ("The ATMP Regulation"). Guidance on the UK's arrangements under the hospital exemption scheme. **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/397738/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf**

Specialist Pharmacy Service. Requirement for Governance and Preparation of Gene Therapy Medicinal Products: Pan UK Pharmacy Working Group for ATMPs. Version 2. Published 30th October 2019. Available from **https://www.sps.nhs.uk/wp-content/uploads/2019/09/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-issue-2.pdf**

Health and Safety Executive. The Genetically Modified Organisms (Contained Use) Regulations 2014. 5th edition, published 2014. **http://www.hse.gov.uk/pubns/books/l29.htm**